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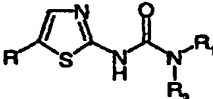
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(21) International Application Number: PCT/EP99/08307 (22) International Filing Date: 27 October 1999 (27.10.1999) (30) Priority Data: 9823873.6 30 October 1998 (30.10.1998) GB (60) Parent Application or Grant PHARMACIA & UPJOHN S.P.A. [/]; O. PEVARELLO, Paolo [/]; O. AMICI, Raffaella [/]; O. TRAQUANDI, Gabriella [/]; O. VILLA, Manuela [/]; O. VULPETTI, Anna [/]; O. ISACCHI, Antonella [/]; O. PEVARELLO, Paolo [/]; O. AMICI, Raffaella [/]; O. TRAQUANDI, Gabriella [/]; O. VILLA, Manuela [/]; O. VULPETTI, Anna [/]; O. ISACCHI, Antonella [/]; O.		Published
(54) Title: 2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS (54) Titre: DERIVES DE 2-UREIDOTHIAZOLS, LEUR PROCEDE DE PREPARATION ET LEUR UTILISATION COMME AGENTS ANTITUMORAUX		
(57) Abstract <p>Compounds which are 2-ureido-1, 3-thiazole derivatives of formula (I) wherein R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from: i) straight or branched C₁-C₆ alkyl; ii) C₂-C₆ cycloalkyl; iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R₁ is an optionally substituted group selected from: i) straight or branched C₁-C₆ alkyl; ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring; iii) aryl or arylcarbonyl; iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R₂ is hydrogen, a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded, R₁ and R₂ form a substituted or unsubstituted group selected from: i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; are useful for treating cell proliferative disorders associated with an altered cell dependent kinase activity.</p> (57) Abrégé <p>L'invention concerne des composés qui sont des dérivés de 2-uréidothiazols de formule (I) dans laquelle R représente un atome d'halogène, un groupe nitro, un groupe amino éventuellement substitué, ou il représente un groupe, également éventuellement substitué, sélectionné parmi i) alkyle C₁-C₆; ii) cycloalkyle C₂-C₆; iii) aryle ou arylalkyle comportant de 1 à 6 atomes de carbone dans la chaîne alkyle linéaire ou ramifiée; R₁ représente un groupe éventuellement substitué sélectionné parmi i) alkyle C₁-C₆ linéaire ou ramifié; ii) un noyau carbocyclique à 3 à 6 chaînons ou hétérocyclique à 5 à 7 chaînons; iii) aryle ou arylcarbonyl; iv) arylalkyle comportant de 1 à 6 atomes de carbone dans la chaîne alkyle; R₂ représente hydrogène, un groupe alkyle C₁-C₄, alcényle C₂-C₄ ou alcynyle linéaires ou ramifiés; ou, avec l'atome d'azote auquel ils sont liés, R₁ et R₂ forment un groupe substitué ou non, sélectionné parmi i) un composé hétérocyclique à 5 à 7 chaînons éventuellement benzocondensé ou ponté; ou ii) un composé spiro-hétérocyclique à 9 à 11 chaînons; ou un sel pharmaceutiquement acceptable desdits composés de l'invention. Ces composés et leurs sels servent au traitement des troubles cellulaires prolifératifs liés à une activité de la kinase dépendant de modifications cellulaires.</p>		

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<p>(21) International Application Number: PCT/EP99/08307 (22) International Filing Date: 27 October 1999 (27.10.99) (30) Priority Data: 9823873.6 30 October 1998 (30.10.98) GB (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): PEVARELLO, Paolo [IT/IT]; Piazza San Pietro in Ciel d'Oro, 7/A, I-27100 Pavia (IT). AMICI, Raffaella [IT/IT]; Via N. Rocca, 11, I-29100 Piacenza (IT). TRAQUANDI, Gabriella [IT/IT]; Via F. Cilea, 106, I-20151 Milano (IT). VILLA, Manuela [IT/IT]; Via San Bernardino, 12, I-22040 Lurago d'Erba (IT). VULPETTI, Anna [IT/IT]; Via Voltorno Portici/2 80, I-20047 Brugherio (IT). ISACCHI, Antonella [IT/IT]; Via Montecatini, 14, I-20144 Milano (IT).</p>	<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>	
<p>(54) Title: 2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS</p>		
<div style="text-align: center;">  <p>(I)</p> </div>		
<p>(57) Abstract</p> <p>Compounds which are 2-ureido-1, 3-thiazole derivatives of formula (I) wherein R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from: i) straight or branched C₁-C₆ alkyl; ii) C₃-C₆ cycloalkyl; iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R₁ is an optionally substituted group selected from: i) straight or branched C₁-C₆ alkyl; ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring; iii) aryl or arylcarbonyl; iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R₂ is hydrogen, a straight or branched C₁-C₄ alkyl or C₂-C₄ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded, R₁ and R₂ form a substituted or unsubstituted group selected from: i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; are useful for treating cell proliferative disorders associated with an altered cell dependent kinase activity.</p>		

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Description

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**2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR
PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS**

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The present invention relates to 2-ureido-thiazole derivatives and, more in particular, it relates to 2-ureido-1,3-thiazoles, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents, particularly in the treatment of cancer and cell proliferative disorders.

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Several cytotoxic drugs such as, e.g. fluorouracil (5-FU), doxorubicin and camptothecins result to damage DNA or to affect cellular metabolic pathways and thus cause, in many cases, an indirect block of the cell cycle.

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Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.

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In this respect, compounds capable of being highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

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It is well known in the art that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk).

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In their turn, the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.

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A normal progression through the cell cycle is controlled by the coordinated activation and inactivation of different cyclin/cdk complexes. In G1, both cyclin D/cdk4 and cyclin E/cdk2 are thought to mediate the onset of S-phase. Progression through S-phase requires the activity of cyclin A/cdk2 whereas the activation of cyclin A/cdc2 (cdk1) and cyclin B/cdc2 are required for the onset of metaphases.

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5 For a general reference to cyclins and cyclin-dependent
kinases see, for instance, Kevin R. Webster et al. in Exp.
Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.

10 5 Checkpoint controls are defective in tumor cells due, in
part, to dysregulation of cdk activity. For example,
altered expression of cyclin E and cdk's has been observed
15 in tumor cells, and deletion of the cdk inhibitor p27 KIP
gene in mice has been shown to result in a higher incidence
20 of cancer.

Increasing evidence supports the idea that the cdks are
rate-limiting enzymes in cell cycle progression and, as
20 such, represent molecular targets for therapeutic
intervention. In particular, the direct inhibition of
15 cdk/cyclin kinase activity should be helpful in restricting
the unregulated proliferation of a tumor cell.

25 It has now been found that the 2-ureido-1,3-thiazoles of
the invention are endowed with cdk/cyclin kinase inhibitory
20 activity and are thus useful in therapy as antitumor agents
whilst lacking, in terms of both toxicity and side effects,
30 the aforementioned drawbacks known for currently available
antitumor drugs.

More specifically, the compounds of this invention are
35 25 useful in the treatment of a variety of cancers including,
but not limited to: carcinoma such as bladder, breast,
colon, kidney, liver, lung, including small cell lung
cancer, esophagus, gall-bladder, ovary, pancreas, stomach,
40 cervix, thyroid, prostate, and skin, including squamous
cell carcinoma; hematopoietic tumors of lymphoid lineage,
including leukemia, acute lymphocytic leukemia, acute
lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma,
45 Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell
lymphoma and Burkett's lymphoma; hematopoietic tumors of
35 myeloid lineage, including acute and chronic myelogenous
leukemias, myelodysplastic syndrome and promyelocytic
leukemia; tumors of mesenchymal origin, including
50 fibrosarcoma and rhabdomyosarcoma; tumors of the central

5 and peripheral nervous system, including astrocytoma,
neuroblastoma, glioma and schwannomas; other tumors,
including melanoma, seminoma, teratocarcinoma,
10 osteosarcoma, xenoderma pigmentosum, keratocanthoma,
5 thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cdk5 in the regulation of cellular
proliferation, these 2-ureido-1,3-thiazole derivatives are
15 also useful in the treatment of a variety of cell
10 proliferative disorders such as, for instance, benign
prostate hyperplasia, familial adenomatosis, polyposis,
neuro-fibromatosis, psoriasis, vascular smooth cell
20 proliferation associated with atherosclerosis, pulmonary
fibrosis, arthritis, glomerulonephritis and post-surgical
15 stenosis and restenosis.

The compounds of the invention can be useful in the
treatment of Alzheimer's disease, as suggested by the fact
25 that cdk5 is involved in the phosphorylation of tau protein
(*J.Biochem.*, 117, 741-749, 1995).

20 The compounds of this invention, as modulators of
apoptosis, could be useful in the treatment of cancer,
30 viral infections, prevention of AIDS development in HIV-
infected individuals, autoimmune diseases and
neurodegenerative disorder.

35 25 The compounds of this invention could be useful in
inhibiting tumor angiogenesis and metastasis.

The compounds of this invention may also act as inhibitors
40 of other protein kinases, e.g. protein kinase C, her2,
30 raf1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF
receptor, PI3 kinase, weel kinase, Src, Abl and thus be
effective in the treatment of diseases associated with
45 other protein kinases.

35 Several 2-ureido-1,3-thiazole derivatives are known in the
art, particularly as herbicides or as synthetic
50 intermediates for preparing herbicides [see, for a general

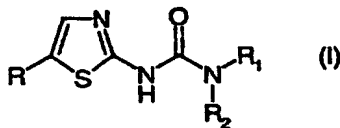
reference, US 3,726,891 in the name of Shell Co., and C.A. 83(1975):114381).

Just few examples among them are N'-methyl- and N'-ethyl-N-(5-bromo-2-thiazolyl)-urea; N'-methyl-, N'-ethyl- or N'-phenyl-N-(5-chloro-2-thiazolyl)-urea; N-(5-chloro-2-thiazolyl)-N',N'-dimethyl-urea; N-(5-bromo-2-thiazolyl)-N',N'-dimethyl-urea; N'-methyl- and N'-phenyl-N-(5-methyl-2-thiazolyl)-urea.

Other 2-ureido-1,3-thiazole derivatives have been described in the art as therapeutic agents.

Among them are N-methyl- and N-phenyl-N'-(5-chloro-2-thiazolyl)-urea which have been described as sedative and antiinflammatory agents in FR M. 7428 (Melle-bezons) or N-[4-(5-oxazolyl)phenyl]-N'-(5-methyl-2-thiazolyl)-urea, described as inosine 5'-monophosphate dehydrogenase inhibitor (IMPDH) in WO 97/40028 (Vertex Pharmaceuticals Inc.).

Accordingly, the present invention provides the use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) C₁-C₆ cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- i) straight or branched C₁-C₆ alkyl;

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- 5 ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- 10 iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;
- 5 R_1 is hydrogen, a straight or branched C_1 - C_6 alkyl or C_1 - C_6 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,
- 15 R_1 and R_2 form a substituted or unsubstituted group selected from:
- 10 i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- 20 ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; in the
- 15 manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase
- 25 activity.

20 According to a preferred embodiment of the invention, the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral

30 infections, auto-immune diseases or neurodegenerative disorders.

35 Preferably, the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral

40 nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma,

30 thyroid follicular cancer and Kaposi's sarcoma.

45 According to another preferred embodiment of the invention, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial

35 adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with

50 atherosclerosis, pulmonary fibrosis, arthritis

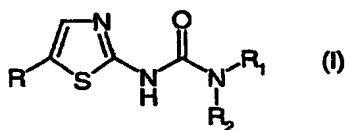
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glomerulonephritis and post-surgical stenosis and restenosis.

In addition, being useful in the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity, hence cell cycle inhibition or cdk/cyclin dependent inhibition, the compounds of formula (I) of the invention also enable tumor angiogenesis and metastasis inhibition.

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as antiinflammatory, sedative and analgesic agents.

Therefore, it is a further object of the present invention a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) C₁-C₆ cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;

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iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₆ alkyl or C₁-C₆ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R₁ and R₂ form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

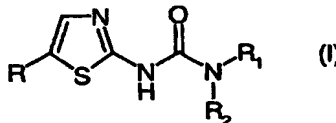
for use as a medicament; provided that:

a) when R is a chlorine atom and R₁ is hydrogen, then R₁ is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R₁ is hydrogen, then R₁ is not 4-(5-oxazolyl)phenyl.

Among the compounds of formula (I) above reported, several derivatives result to be novel.

Therefore, the present invention further provides a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C₁-C₆ alkyl;

iii) C₁-C₆ cycloalkyl;

iv) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

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- 5 i) straight or branched C₁-C₆ alkyl;
ii) 3 to 6 membered carbocycle or 5 to 7 membered
heterocycle ring;
iii) aryl or arylcarbonyl;
10 5 iv) arylalkyl with from 1 to 6 carbon atoms within the
straight or branched alkyl chain;
R₁ is hydrogen, a straight or branched C₁-C₆ alkyl or C₂-C₆
alkenyl or alkynyl group; or, taken together with the
15 nitrogen atom to which they are bonded,
10 R₁ and R₂ form a substituted or unsubstituted group selected
from:
i) an optionally benzocondensed or bridged 5 to 7
20 membered heterocycle; or
ii) a 9 to 11 membered spiro-heterocyclic compound; or a
15 pharmaceutically acceptable salt thereof; provided that:
a) when R is chlorine or bromine and R₁ is hydrogen, then
25 R₁ is not unsubstituted C₁-C₆ alkyl, phenyl,
trifluoromethylphenyl or an optionally substituted
phenylcarbonyl;
20 b) when R is methyl and R₁ is hydrogen, then R₁ is not
methyl, phenyl or 4-(5-oxazolyl)phenyl;
30 c) when R is nitrophenyl and R₁ is hydrogen, then R₁ is
not haloalkyl;
d) when R is bromine or chlorine, then R₁ and R₂ are not
35 25 both methyl groups.

The compounds of formula (I) may have asymmetric carbon
atoms and may therefore exist either as racemic admixtures
40 or as individual optical isomers.

30 Accordingly, all the possible isomers and their admixtures
and of both the metabolites and the pharmaceutically
acceptable bio-precursors (otherwise referred to as pro-
45 drugs) of the compounds of formula (I), as well as the uses
thereof, are also within the scope of the present
35 invention.

- 5 In the present description, unless otherwise specified,
with the term halogen atom we intend a chlorine, bromine,
fluorine or iodine atom.
- 10 5 With the term optionally substituted amino group we intend
an amino group wherein one or both hydrogen atoms are
optionally replaced by other substituents which are the
same or different, as set forth below.
- 15 10 With the term straight or branched C₁-C₆ alkyl we intend a
group such as, for instance, methyl, ethyl, n.propyl,
isopropyl, n.butyl, isobutyl, sec-butyl, tert-butyl,
20 n.pentyl, n.hexyl and the like.
- 15 15 With the term straight or branched C₂-C₆ alkenyl or alkynyl
group we intend a group such as, for instance, vinyl,
25 allyl, isopropenyl, 1-, 2- or 3-butenyl, isobutylenyl,
ethynyl, 1- or 2-propynyl, butynyl and the like.
- 20 20 With the term C₃-C₆ cycloalkyl we intend a cyclopropyl,
30 cyclobutyl, cyclopentyl or cyclohexyl group.
- With the term aryl, either as such or as arylalkyl,
arylcarbonyl and the like, we intend a mono-, bi- or poly-
35 25 either carbocyclic as well as heterocyclic hydrocarbon with
from 1 to 4 ring moieties, either fused or linked to each
other by single bonds, wherein at least one of the
carbocyclic or heterocyclic rings is aromatic.
- 40 Examples of aryl groups are phenyl, biphenyl, α - or β -
30 naphthyl, tetrahydronaphthyl, indenyl, dihydroindenyl,
pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl,
isoindolyl, dihydroisoindolyl, imidazolyl, imidazopyridyl,
45 benzimidazolyl, dihydrobenzimidazolyl, 1,2-
methylenedioxyphenyl, thiazolyl, isothiazolyl,
35 benzothiazolyl, pyrrolyl, pyrazolyl, furyl,
benzotetrahydrofuranlyl, benzofuranlyl, dihydrobenzofuranlyl,
50 oxazolyl, isoxazolyl, thienyl, benzothienyl, tetrazolyl,

5 quinolinyl, isoquinolinyl, dihydroisoquinolinyl,
quinoxalinyl, dihydroquinoxalinyl, oxadiazolyl,
tetrahydrobenzodiazepin-yl and the like.

10 5 With the term 3 to 6 membered carbocycle, hence
encompassing but not limited to C₃-C₆ cycloalkyl groups, we
also intend an unsaturated carbocyclic hydrocarbon such as,
for instance, cyclopentylene or cyclohexylene.

15 10 With the term 5 to 7 membered heterocycle, hence
encompassing aromatic heterocycles also referred to as aryl
groups, we further intend a saturated or partially
20 unsaturated 5 to 7 membered carbocycle wherein one or more
carbon atoms are replaced by heteroatoms such as nitrogen,
15 oxygen and sulphur.

25 Examples of 5 to 7 membered heterocycles, optionally
benzocondensed or further substituted, are 1,3-dioxolane,
pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine,
pyrazoline, piperidine, piperazine, N-alkyl-piperazine,
20 morpholine, tetrahydrofuran, and the like.

30 With the term bridged heterocycles we intend a system at
least comprising two rings, one of which being a nitrogen
containing heterocycle, having two or more atoms in common
35 25 such as, for instance, azabicyclo[3.2.2]nonane.

40 With the term 9 to 11 membered spiro heterocycle we intend
a system at least comprising two rings, one of which being
a nitrogen containing heterocycle, having one carbon atom
30 in common such as, for instance, 1,4-dioxo-8-
azaspiro[4.5]decane and 1,3,8-triazaspiro[4.5]decane.

45 According to the above indicated substituent meanings, any
of the above R, R₁ and R₂ groups may be optionally
35 substituted in any of the free positions by one or more
groups, for instance 1 to 6 groups, selected from: halogen,
50 nitro, oxo groups (=O), carboxy, cyano, alkyl,
perfluorinated alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

5 heterocyclyl, amino groups and derivatives thereof such as,
for instance, alkylamino, alkoxycarbonylalkylamino,
dialkylamino, arylamino, diarylamino, alkylsulfonylamino or
aryluireido; carbonylamino groups and derivatives thereof
10 5 such as, for instance, formylamino, alkylcarbonylamino,
alkenylcarbonylamino, arylcarbonylamino,
alkoxycarbonylamino; oxygen-substituted oximes such as, for
instance, alkoxycarbonylalkoxyimino or alkoxyimino; hydroxy
15 groups and derivatives thereof such as, for instance,
10 alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy,
cycloalkenyloxy; carbonyl groups and derivatives thereof
such as, for instance, alkylcarbonyl, arylcarbonyl,
20 alkoxycarbonyl, aryloxy carbonyl, cycloalkyloxy carbonyl,
aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl;
15 sulfurated derivatives such as, for instance, alkylthio,
arylthio, alkylsulphonyl, arylsulphonyl, alkylsulphinyl,
25 arylsulphinyl, arylsulphonyloxy, aminosulfonyl,
alkylaminosulphonyl or dialkylaminosulphonyl. In their
turn, whenever appropriate, each of the above possible
20 substituents on R, R₁ and R₂ may be further substituted by
one or more of the aforementioned groups.
30 Examples of compounds of formula (I) wherein R, R₁ and R₂
groups are substituted by one or more of the aforementioned
substituents which, in their turn, are optionally further
35 25 substituted as set forth above, are given below.

Pharmaceutically acceptable salts of the compounds of
formula (I) are the acid addition salts with inorganic or
40 organic, e.g. nitric, hydrochloric, hydrobromic, sulphuric,
30 perchloric, phosphoric, acetic, trifluoroacetic, propionic,
glycolic, lactic, oxalic, malonic, malic, maleic, tartaric,
citric, benzoic, cinnamic, mandelic, methanesulphonic,
45 isethionic and salicylic acid, as well as the salts with
inorganic or organic bases, e.g. alkali or alkaline-earth
35 metals, especially sodium, potassium, calcium or magnesium
hydroxides, carbonates or bicarbonates, acyclic or cyclic
50 amines, preferably methylamine, ethylamine, diethylamine,
triethylamine or piperidine.

- 12 -

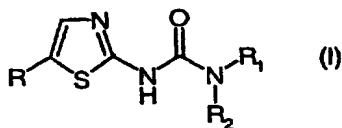
The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

Preferred compounds of the invention are the compounds of formula (I) wherein R is a halogen atom, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₁ is hydrogen and R₂ is an optionally substituted group selected from alkyl, aryl or arylalkyl.

Even more preferred, within this class, are the compounds of formula (I) wherein R is bromine or chlorine, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₁ is hydrogen and R₂ is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.

Another class of preferred compounds of the invention are the compounds of formula (I)



wherein

R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C₁-C₄ cycloalkyl, straight or branched C₁-C₄ alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, aryl optionally substituted

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by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or carboxy, or R is an aryl group optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or carboxy;

R₁ is a straight or branched C₁-C₆ alkyl group or an aryl group, each optionally substituted as above reported for R;

R₂ is a hydrogen atom; and pharmaceutically acceptable salts thereof;

provided that:

- a) when R is chlorine or bromine then R₁ is not unsubstituted C₁-C₆ alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;
- b) when R is methyl then R₁ is not methyl, phenyl or 4-(5-oxazolyl)phenyl;
- c) when R is nitrophenyl then R₁ is not haloalkyl.

Another class of preferred compounds of formula (I) are those wherein R is a straight or branched C₁-C₆ alkyl group and, together with the nitrogen atom to which they are bonded, R₁ and R₂ form a substituted or unsubstituted, optionally either benzocondensed or bridged 5 to 7 membered heterocycle, or 9 to 11 membered spiro-heterocycle.

Still another class of preferred compounds of formula (I) are those wherein R is a straight or branched C₁-C₆ alkyl group; R₁ is a straight or branched C₁-C₆ alkyl or C₁-C₆ alkenyl or alkynyl group and R₂ is an aryl or arylalkyl group with from 1 to 4 carbon atoms within the straight or branched alkyl chain.

5 Examples of preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, e.g. hydrobromide or hydrochloride salt, are the following:

- 10 5 1) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 2) N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 15 3) N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 4) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
- 10 5) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 6) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 20 7) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 15 8) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;
- 25 9) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 20 10) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 30 11) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 12) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;
- 35 25 13) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 14) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 40 15) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 30 16) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
- 45 17) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 35 18) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
- 50 19) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

- 5 20) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
21) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
10 urea;
5 22) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
23) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
urea;
15 24) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
10 25) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
26) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
20 urea;
27) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
15 urea;
28) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;
25 29) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
20 30) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
31) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
35 32) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;
25 33) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
34) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
40 urea;
30 35) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
36) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;
45 37) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
35 38) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
50

- 5 39) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
40) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-
phenyl)-urea;
10 5 41) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
42) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
15 43) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
10 44) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-
phenyl)-urea;
20 45) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
15 46) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
47) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
25 48) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
49) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;
20 50) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
30 51) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
52) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;
35 25 53) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
urea;
54) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
55) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
40 56) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
urea;
30 57) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
45 58) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
59) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
35 60) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
50 61) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
62) N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;

- 5 63) N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
64) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
65) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
66) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
10 5 67) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
68) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-
urea;
69) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
15 70) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
10 71) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
72) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-
urea;
20 73) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
74) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
15 75) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
76) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-
urea;
25 77) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-
yl)-urea;
20 78) N-(5-bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea;
30 79) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea; N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-
(benzothiophen-2-yl)-urea;
35 25 80) N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine
carboxamide;
81) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
methylphenyl)urea;
40 82) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
fluorophenyl)urea;
30 83) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
cyanophenyl)urea;
45 84) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
cyanophenyl)urea;
35 85) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-
dimethylphenyl)urea;
50 86) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
fluorobenzyl)urea;

- 5 87) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-acetylphenyl)urea;
88) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-acetylphenyl)urea;
10 5 89) 3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;
90) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-isopropylphenyl)urea;
15 91) 3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzamide;
10 92) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
20 93) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-butylphenyl)urea;
15 94) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluoromethylphenyl)urea;
25 95) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-bromophenyl)urea;
96) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyclohexylphenyl)urea;
20 97) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea;
30 98) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;
99) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea;
35 25 100) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;
101) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy[1,1'-biphenyl]-4-yl)urea;
40 30 102) N-(5-isopropyl-1,3-thiazol-2-yl)-3,4-dihydro-2(1H)-isoquinoline carboxamide;
103) N-benzyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-methylurea;
45 104) N-(5-isopropyl-1,3-thiazol-2-yl)-6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinoline carboxamide;
35 105) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)-phenyl]urea;
50

- 5 106) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((3-chloro-6-methyl)phenyl)urea;
107) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea;
10 108) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
109) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((2-methoxy-5-chloro)phenyl)urea;
15 110) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-((2-chloro-4-methoxyphenyl)urea;
10 111) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;
20 112) N-((1,1'-biphenyl)-2-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
15 113) N-ethyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-phenylurea;
114) N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-2-methoxyphenyl]acetamide;
25 115) 2-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-N-phenylbenzamide;
20 116) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;
30 117) N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)phenyl]-N-methyl acetamide;
118) N-(2-((cyclohexyl(methyl)amino)methyl)phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 25 119) N-[3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methoxyphenyl]acetamide;
120) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;
40 121) N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
122) N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
45 123) N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 124) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-methyl-1H-pyrrol-2-yl)ethyl)urea;
50

- 5 125) N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
126) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
10 5 127) n-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide;
128) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-piperidinyl)ethyl)urea;
15 129) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-morpholinyl)ethyl)urea;
10 130) 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
20 131) N-(4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
15 132) 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
25 133) N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
134) N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
20 135) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;
30 136) N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 25 137) N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
138) N-(4-[ethyl(isopropyl)amino]phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
40 139) N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
30 140) 5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-1-phenyl-1H-pyrazole-4-carboxamide;
45 141) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
35 142) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
50 143) n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;

- 5 144) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide;
145) N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
10 146) N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
147) N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
15 148) N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine carboxamide;
20 149) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
150) N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
15 151) N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
25 152) 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
153) N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-3-carboxamide;
30 154) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide;
155) 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
35 156) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;
157) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
40 158) N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
30 159) 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
45 160) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
35 161) N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
50 162) N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;

- 5 163) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea;
164) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea;
10 165) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;
166) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorobenzyl)urea;
15 167) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea;
10 168) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea;
20 169) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea;
15 170) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
25 171) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-methoxy)benzyl]urea;
172) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-furyl)urea;
20 173) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylsulfonylbenzyl)urea;
30 174) N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 25 175) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea;
176) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
40 177) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethoxybenzyl)urea;
30 178) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
45 179) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
35 180) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea;
50 181) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea;

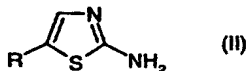
- 5 182) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
- 183) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 10 5 184) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
- 185) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
- 15 186) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 10 187) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
- 20 188) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 15 189) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinolinyl)urea;
- 25 190) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea;
- 191) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea;
- 20 192) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;
- 30 193) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea;
- 194) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphtalenyl)urea;
- 35 25 195) methyl-3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methylbenzoate;
- 196) methyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-3-methylbenzoate;
- 40 197) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea;
- 45 198) ethyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoate;
- 199) (2R)-1-benzyl-2-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)propanamide;
- 35 200) 2-hydroxy-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)benzoic acid;
- 50

- 5 201) 2-chloro-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;
202) 3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;
10 5 203) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;
204) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;
15 205) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea;
10 206) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
20 207) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
15 208) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-benzimidazol-5-yl)urea;
25 209) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea;
210) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea;
20 211) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea;
30 212) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl)urea;
35 25 213) N-(3-iodophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
214) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[3-(3-methoxy-1-propynyl)phenyl]urea;
215) N-(3-[3-(dimethylamino)-1-propynyl]phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
40 216) N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)phenyl]methanesulfonamide;
217) 2-[3-(((5-isopropyl-1,3-thiazol-2-ylamino)carbonyl)amino)anilino]acetamide;
45 218) N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 219) N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
50

- 220) 2-{{[(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl}(2-propynyl)amino)methyl)benzenesulfonamide;
- 221) N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 222) N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 223) N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 224) N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 225) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea;
- 226) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
- 227) N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
- 228) N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
- 229) N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
- 230) N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
- 231) N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
- 232) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;
- 233) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;
- 234) N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;
- 235) N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;
- 236) N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;
- 237) N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

The compounds of formula (I) object of the present invention and the salts thereof can be obtained, for instance, by a process comprising:

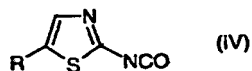
- a) when R₁ is a hydrogen atom
reacting a compound of formula (II)



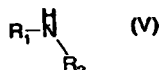
wherein R is as defined above, with a compound of formula (III)



wherein R_1 is as defined above; or
 b) when R_2 is a hydrogen atom or has the meanings above
 reported
 reacting a compound of formula (IV)

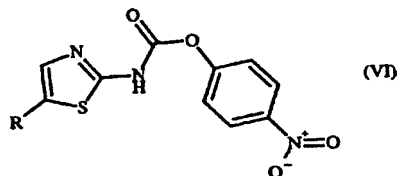


wherein R is as defined above, with a compound of
 formula (V)

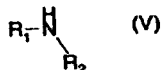


wherein R_1 and R_2 are as defined above; and, if
 desired, converting a 2-ureido-1,3-thiazole derivative of
 formula (I) into another such derivative of formula (I),
 and/or into a salt thereof.

The compounds of formula (I) can alternatively be obtained
 by a process comprising:
 reacting a compound of formula (II) wherein R is as
 described above with 4-nitrophenyl-chloroformate, or a
 polymer supported form of it, thus obtaining a compound of
 formula (VI), or a polymer supported form of it,

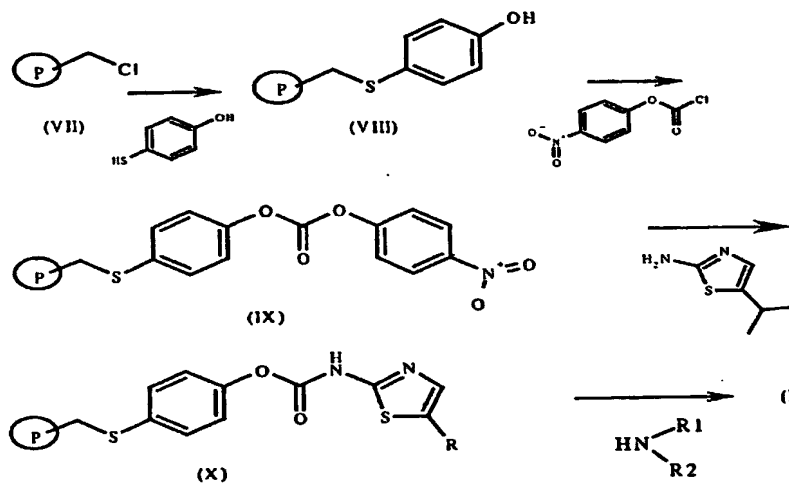


wherein R is as described above; and reacting a compound of
 formula (VI) with a compound of formula (V)



wherein R_1 and R_2 are as described above; and, if desired,
 converting a 2-ureido-1,3-thiazole derivative of formula
 (I), or a polymer supported form of it, into another such
 derivative of formula (I), and/or into a salt thereof.

More particularly, when referring to the process performed by using polymer supported species, the synthetic pathway can be summarized as follows:



In addition, when referring to the process performed by using polymer supported species, conventional reaction conditions are well known to the skilled man.

It is further clear to the man skilled in the art that if the compound of formula (I), prepared according to the above processes, is obtained as an admixture of isomers, their separation into the single isomers of formula (I) according to conventional techniques is still within the scope of the present invention.

Likewise, the conversion into the free 2-ureido-1,3-thiazole derivative (I) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

The above process-variants are analogy processes which can be carried out according to well known methods.

5 The reaction between a compound of formula (II) and a
compound of formula (III), or the reaction between a
compound of formula (IV) and a compound of formula (V), can
10 be carried out in a suitable solvent such as, for instance,
5 dichloromethane, chloroform, tetrahydrofuran, diethyl
ether, 1,4-dioxane, acetonitrile, toluene or acetone, at a
temperature ranging from room temperature to reflux for a
time varying between about 1 to 96 hours.

15 The reaction of a compound of formula (II) to give a
10 compound of formula (VI) is carried out with 4-
nitrophenylchloroformate, or a polymer supported form of
it, in the presence of a tertiary base such as, for
20 instance, triethylamine, N-methylmorpholine, N,N-
diisopropylethylamine or pyridine, in a suitable solvent
15 such as toluene, dichloromethane, chloroform, diethylether,
tetrahydrofuran, acetonitrile, dioxane or N,N-
25 dimethylformamide, at a temperature ranging from
approximately -10°C to room temperature.

The reaction between a compound of formula (VI) and a
20 compound of formula (V) to give a compound of formula (I)
30 can be carried out in a suitable solvent such as toluene,
dichloromethane, chloroform, diethylether, tetrahydrofuran,
acetonitrile, 1,4-dioxane or N,N-dimethylformamide, at a
temperature ranging from about room temperature to reflux.

35 In the above-mentioned scheme, as far as the solid phase
approach is concerned, compound (VIII) can be prepared by
reacting compound (VII) with 4-mercaptophenol in the
presence of a base such as potassium tert-butoxide,
40 potassium carbonate or potassium sodium hydroxide and in a
30 suitable solvent such as N,N-dimethylformamide at a
temperature ranging from 40 to 60 °C. The reaction between
compound (VIII) and p-nitrophenylchloroformate to give
45 compound (IX) can be carried out in presence of a base such
as N-methylmorpholine, triethylamine or N,N-
35 diisopropylethylamine in a suitable solvent such as
dichloromethane, chloroform, 1,4-dioxane or N,N-
50 dimethylformamide at room temperature.

5 The reaction between compound (IX) and the compound of
formula (II), wherein R is as described above, thus
obtaining the compound of formula (X), can be carried out
10 in a suitable solvent such as dichloromethane, chloroform,
5 toluene or N,N-dimethylformamide at room temperature for a
time varying between about 2 to 22 hours.

The reaction between the compound of formula (X), wherein R
is as described above, and the compound of formula (V)
15 wherein R₁ and R₂ are as described above, thus obtaining the
10 compound of formula (I), can be carried out in the presence
of a base such as triethylamine, N,N-diisopropylethylamine
or N-methylmorpholine in a suitable solvent such as
20 toluene, acetonitrile or N,N-dimethylformamide at a
temperature ranging from room temperature to 100°C.

15 Also the optional conversion of a compound of formula (I)
into another compound of formula (I) can be carried out
25 according to known methods.

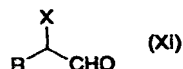
As an example, the nitro group of a compound of formula (I)
may be converted into an amino group by treatment, for
20 example, with stannous chloride in concentrated
30 hydrochloric acid and by using, if necessary, an organic
solvent such as acetic acid, 1,4-dioxane and
tetrahydrofuran, at a temperature varying between room
temperature and about 100°C.

35 Likewise, an alkylthio or an arylthio group may be
converted into the corresponding alkylsulfonyl and
arylsulfonyl group by reaction, for example, with m-
40 chloroperbenzoic acid in a suitable solvent such as
dichloromethane or chloroform, at a temperature varying
30 from about -5°C and room temperature.

The optional salification of a compound of formula (I) or
the conversion of a salt into the free compound as well as
45 the separation of a mixture of isomers into the single
isomers may be carried out by conventional methods.

35 The compounds of formula (II) and (IV) according to the
above processes are known compounds or can be obtained
50 according to known methods.

For example, a compound of formula (II) wherein R is as defined above can be obtained by reacting a compound of formula (XI)



wherein X is a bromine or chlorine atom, with thiourea in a suitable solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane or toluene, at a temperature varying between room temperature and reflux, for a suitable time ranging from about 1 hour to about 24 hours.

A compound of formula (IV) can be obtained, for instance, by reacting a compound of formula (II) wherein R is as defined above with bis(trichloromethyl) carbonate or trichloromethyl chloroformate in the presence, if necessary, of a tertiary base such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as dichloromethane, chloroform or toluene, at a temperature ranging from about -20°C to reflux.

The compounds of formula (III), (V) and (XI) are well-known commercially available compounds or, alternatively, may be conventionally prepared according to known methods in organic chemistry.

When preparing the compounds of formula (I) according to the process object of the present invention, optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

Pharmacology

The compounds of formula (I) are active as cdk/cyclin inhibitors as they gave positive results when tested according to the following procedure.

5 The compounds of formula (I) are therefore useful to
restrict the unregulated proliferation of tumor cells,
hence in therapy in the treatment of various tumors such
as, for instance, carcinomas, e.g. mammary carcinoma, lung
10 carcinoma, bladder carcinoma, colon carcinoma, ovary and
endometrial tumors, sarcomas, e.g. soft tissue and bone
sarcomas, and the hematological malignancies such as, e.g.,
leukemias.

15 In addition, the compounds of formula (I) are also useful
10 in the treatment of other cell proliferative disorders such
as psoriasis, vascular smooth cell proliferation associated
with atherosclerosis and post-surgical stenosis and
restenosis and in the treatment of Alzheimer's disease.

15 The inhibiting activity of putative cdk/cyclin inhibitors
and the potency of selected compounds was determined
25 through a method of assay based on the use of the
MultiScreen-PH 96 well plate (Millipore), in which a
phosphocellulose filter paper was placed at each well
20 bottom allowing binding of positive charged substrate after
a washing/filtration step.

30 When a radioactivity labelled phosphate moiety was
transferred by the ser/threo kinase to the filter-bound
histone, light emitted was measured in a scintillation
25 counter.

35 The inhibition assay of cdk2/Cyclin A activity was
performed according to the following protocol:

40 Kinase reaction: 1.5 μ M histone H1 substrate, 25 μ M ATP
30 (0.5 μ Ci P^{32} -ATP), 30 ng Cyclin A/ckd2 complex, 10 μ M
inhibitor in a final volume of 100 μ l buffer (TRIS HCl 10
45 mM pH 7.5, MgCl, 10 mM, 7.5 mM DTT) were added to each well
of a 96 U bottom well plate. After 10 min at 37 °C
incubation, reaction was stopped by 20 μ l EDTA 120 mM.

35

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Capture: 100 μ l were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μ l/well PBS $\text{Ca}^{++}/\text{Mg}^{++}$ free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 μ l/well scintillant were added and ^{32}P labelled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analysed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition ≥ 50 % were further analysed in order to study and define potency (IC_{50}) as well as the kinetic-profile of inhibitor through K_i calculation.

IC_{50} determination: the protocol used was the same described above, where inhibitors were tested at concentrations ranging from 0.0045 to 10 μM . Experimental data were analyzed by the computer program GraphPad Prizm.

K_i calculation: either the concentration of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μM for ATP (containing proportionally diluted $\text{P}^{32}\text{Y-ATP}$) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analysed by the computer program SigmaPlot for K_i determination, using a random bireactant system equation:

$$v = \frac{V_{\max} \frac{(A)(B)}{aK_A K_B}}{1 + \frac{(A)}{K_A} + \frac{(B)}{K_B} + \frac{(A)(B)}{aK_A K_B}}$$

where A=ATP and B=histone H1.

5 Following the method above described, a representative
compound of formula (I) of the invention, which is N-(5-
isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea,
10 5 showed an inhibiting activity towards the cdk2/cyclin A
complex corresponding to 0.56 μ M (IC50).

15 In addition, the inhibiting activity of putative cdk/cyclin
inhibitors and the potency of selected compounds was
determined through a method of assay based on the use of a
10 SPA (Scintillation Proximity Assay) 96 well plate assay.
The assay is based on the ability of streptavidin coated
SPA beads to capture a biotinylated peptide derived from a
20 phosphorylation site of histone.

15 When a radioactivity labelled phosphate moiety was
transferred by the ser/threo kinase to the biotinylated
histone peptide, light emitted was measured in a
25 scintillation counter.

The inhibition assay of cdk5/p25 activity was performed
according to the following protocol:

20 **Kinase reaction:** 1.0 μ M biotinylated histone peptide
substrate, 0.25 uCi P33g-ATP, 4 nM cdk2/p25 complex, 0-100
30 μ M inhibitor in a final volume of 100 μ l buffer (Hepes 20
mM pH 7.5, MgCl2 15 mM, 1 mM DTT) were added to each well
of a 96 U bottom well plate. After 20 min at 37 °C
35 25 incubation, the reaction was stopped by the addition of 500
ug SPA beads in phosphate-buffered saline containing 0.1%
Triton X-100, 50 μ M ATP and 5 mM EDTA. The beads were
40 allowed to settle, and the radioactivity incorporated in
the 33P-labelled peptide was detected in a Top Count
30 scintillation counter.

45 **Results:** Data were analyzed and expressed as % Inhibition
using the formula:

$$100 \times (1 - (\text{Unknown} - \text{Bkgd}) / (\text{Enz. Control} - \text{Bkgd}))$$

35 IC50 values were calculated using a variation of the four
parameter logistics equation:
50

5
$$Y = 100/[1 + 10^{((\text{LogEC50} - X) \cdot \text{Slope})}]$$

Where X = log(uM) and Y = % Inhibition.

10 5 The compounds of formula (I) are therefore useful to
restrict the unregulated proliferation of tumor cells,
hence in therapy in the treatment of various tumors such
as, for instance, carcinomas, e.g. mammary carcinoma, lung
15 carcinoma, bladder carcinoma, colon carcinoma, ovary and
20 10 endometrial tumors, sarcomas, e.g. soft tissue and bone
sarcomas, and the hematological malignancies such as, e.g.,
leukemias.

20 In addition, the compounds of formula (I) are also useful
in the treatment of other cell proliferative disorders such
15 as psoriasis, vascular smooth cell proliferation associated
with atherosclerosis and post-surgical stenosis and
25 restenosis and in the treatment of Alzheimer's disease.

30 20 The compounds of the present invention can be administered
either as single agents or, alternatively, in combination
with known anticancer treatments such as radiation therapy
or chemotherapy regimen in combination with cytostatic or
cytotoxic agents.

35 25 As an example, the above compounds can be administered in
combination with one or more chemotherapeutic agents such
as, for instance, taxane, taxane derivatives, CPT-11,
camptothecin derivatives, anthracycline glycosides, e.g.
doxorubicin or epirubicin, etoposide, navelbine,
40 vinblastine, carboplatin, cisplatin and the like,
30 optionally within liposomal formulations thereof.

45 The compounds of formula (I) of the present invention,
suitable for administration to a mammal, e.g. to humans,
can be administered by the usual routes and the dosage
35 level depends upon the age, weight, conditions of the
patient and the administration route.

5 For example, a suitable dosage adopted for oral
administration of a compound of formula (I) may range from
about 10 to about 500 mg pro dose, from 1 to 5 times daily.
10 The compounds of the invention can be administered in a
5 variety of dosage forms, e.g. orally, in the form of
tablets, capsules, sugar or film coated tablets, liquid
solutions or suspensions; rectally in the form of
suppositories; parenterally, e.g. intramuscularly, or by
15 intravenous and/or intrathecal and/or intraspinal injection
10 or infusion.

20 The present invention also includes pharmaceutical
compositions comprising a compound of formula (I), or a
pharmaceutically acceptable salt thereof, in association
15 with a pharmaceutically acceptable excipient (which can be
a carrier or a diluent).

25 The pharmaceutical compositions containing the compounds of
the invention are usually prepared following conventional
methods and are administered in a pharmaceutically suitable
20 form.

30 For example, the solid oral forms may contain, together
with the active compound, diluents, e.g. lactose, dextrose,
saccharose, sucrose, cellulose, corn starch or potato
starch; lubricants, e.g. silica, talc, stearic acid,
35 magnesium or calcium stearate, and/or polyethylene glycols;
25 binding agents, e.g. starches, arabic gum, gelatine,
methylcellulose, carboxymethylcellulose or polyvinyl
pyrrolidone; disaggregating agents, e.g. a starch, alginic
40 acid, alginates or sodium starch glycolate; effervescing
30 mixtures; dyestuffs; sweeteners; wetting agents such as
lecithin, polysorbates, laurylsulphates; and, in general,
non-toxic and pharmacologically inactive substances used in
45 pharmaceutical formulations. • Said pharmaceutical
preparations may be manufactured in known manner, for
35 example, by means of mixing, granulating, tableting,
sugar-coating, or film-coating processes.

50 The liquid dispersions for oral administration may be e.g.
syrups, emulsions and suspensions.

5 The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

10 5 The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

15 The suspension or solutions for intramuscular injections may contain, together with the active compound, a
20 10 pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile
25 15 water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

30 25 The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

35 25 The following examples illustrate but do not limit the present invention.

Example 1

Preparation of methyl cyclopropylacetate

40 30 Cyclopropylacetic acid (1.08 g; 10.57 mmol) was dissolved in 50 ml of methanol. The solution was cooled to 0°C and 5 ml of sulfuric acid 96% were dropped under stirring. The solution was maintained at room temperature overnight and then poured onto ice-water, basified with 30 % ammonium
45 hydrate and finally extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated
50 35 to dryness to give 1.1 g of an oily product (90% yield) which was used as such without any further purification.

Example 2

Preparation of 2-cyclopropylethanol

Sodium (85 mg; 0.004 mmol) was dissolved in 50 ml of methanol and 8.7 g (0.23 mol) of sodium borohydride were added. A solution of 3.7 g (0.032 mol) of methyl cyclopropylacetate, prepared according to example 1, in 20 ml of methanol was dropped to the mixture under stirring. The reaction was maintained at reflux for 6 hours, then 300 ml of brine were added and the crude extracted with methylene chloride.

The organic layer was dried over sodium sulfate and evaporated to dryness to give 1.52 g (55% yield) of the title compound.

Example 3Preparation of a compound of formula (VI): 2-cyclopropylethanol

Oxalyl chloride (1.24 ml; 14.18 mmol) was dissolved in 10 ml of methylene chloride; after cooling to -60°C a solution of 1.02 g (11.9 mmol) of 2-cyclopropylethanol, prepared according to example 2, in 10 ml of methylene chloride was added dropwise. The mixture was maintained under stirring for 30 minutes at the same temperature, then 8.3 ml (59.5 mmol) of triethylamine were added.

After 2 hours at 0°C water was added. The mixture was diluted with methylene chloride and washed successively with 1M hydrochloric acid, water, saturated sodium bicarbonate and finally with brine. The organic layer was dried over sodium sulfate and evaporated to dryness to give 0.31 g (30% yield) of the title compound.

Example 4Preparation of a compound of formula (II): 2-amino-5-isopropyl-1,3-thiazole

3-Methylbutanaldehyde (2 ml; 18.6 mmol) was dissolved in 15 ml of dioxane.

A solution 2% v/v of bromine in dioxane (47.81 ml; 18.6 mmol) was dropped therein at 0°C. The mixture was maintained at room temperature under stirring for 2 hours,

then 2.83 g (37.2 mmol) of thiourea and 10 ml of ethanol were added. After 6 hours at room temperature the solution was evaporated to dryness, the residue was dissolved in methylene chloride and the product extracted with 1M hydrochloric acid; the aqueous layer was made basic by using 30% ammonium hydrate and extracted again with methylene chloride.

The organic phase was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on a silica gel column, eluting with cyclohexane-ethylacetate to give 1.1 g (42% yield) of the title compound.

¹H-NMR (DMSO-d₆) δ ppm: 6.6 (s, 2H, NH₂); 6.58 (s, 1H, thiazole CH); 2.9 (m, 1H, CHMe₂); 1.18 (s, 3H, MeCHMe₂); 1.17 (s, 3H, MeCHMe₂).

By analogous procedures the following compounds can be prepared:

2-amino-5-phenyl-1,3-thiazole; and
2-amino-5-cyclopropyl-1,3-thiazole.

Example 5

Preparation of a compound of formula (I): N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea

Phenylisocyanate (1.7 ml; 15.6 mmol) was added to a solution of 2-amino-5-bromo-1,3-thiazole hydrobromide (4 g; 15.6 mmol) and triethylamine (2.1 ml; 15.6 mmol) in dichloromethane (70 ml), maintained under magnetic stirring at room temperature. After about 4 days, methanol (7 ml) was added and the reaction mixture was then washed with brine, dried over sodium sulfate and evaporated.

The residue was purified by chromatography on silica gel (dichloromethane and then dichloromethane/methanol=90:10) to give 1.9 g (52%) of the title compound as a colourless solid (m.p. 166-169°C/dec.).

¹H-NMR (CDCl₃) δ ppm: 10.50 (bs, 1H, -NHCONHPh); 8.50 (bs, 1H, -NHCONHPh); 7.45 (d, J = 7.6 Hz, 2H, o-Ph hydrogens);

7.36 (dd, J = 7.3 and 7.6 Hz, 2H, m-Ph hydrogens); 7.29 (s, 1H, thiazole CH); 7.16 (t, J = 7.3 Hz, 1H, p-Ph hydrogens).

By analogous procedure, and by starting from the corresponding isocyanate, the following compounds can be prepared:

N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea

¹H-NMR (DMSO-d₆) δ ppm: 10.56 (bs, 1H, -NHCONHPh); 8.99 (bs, 1H, NHCONHPh); 7.77 (s, 1H, thiazole CH); 7.6-7.0 (m, 10H, phenyl);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea
m.p. >200°C

¹H-NMR (DMSO-d₆) δ ppm: 10.58 (bs, 1H, -NHCONHPh); 9.38 (bs, 1H, NHCONHPh); 7.75 (d, 2H, H₃ and H₅ Ph); 7.61 (d, 2H, H₂ and H₆ Ph); 7.21 (s, 2H, SO₂NH₂); 7.02 (s, 1H, thiazole CH); 3.02 (m, 1H, CH(Me)₂); 1.22 (s, 3H, MeCHMe); 1.21 (s, 3H, MeCHMe);

ESI(+)-MS: m/z 341 (100, (M+H)⁺).

N-benzoyl-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

m.p. 217-219°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.27 (d, 6H, J=6.8, CH₂CHCH₃); 3.11 (m, 1H, CH₂CHCH₃); 7.18 (d, 1H, J=0.9, H thiazole); 7.54 (m, 2H, m-phenyl); 7.66 (m, 1H, p-phenyl); 8.00 (m, 2H, o-phenyl); 11.50 (bs, 1H, NH); 11.80 (bs, 1H, NH).

ESI (+)MS: m/z 290 (70, (M+H)⁺; m/z 169 (100, (MH-C₆H₅CONH₂)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea
m.p. 149-150°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₂CHCH₃); 3.06 (m, 1H, CH₂CHCH₃); 3.72 (s, 3H, CH₃); 7.02 (s, 1H, H thiazole); 6.57 (dd, 1H, J=8.3, 2.4, H-4'-phenyl);

6.93 (d, 1H, J=8.3, H-6'-phenyl); 7.18 (m, 2H, H-5', H-2'-phenyl); 8.94 (s, 1H, NH); 10.35 (bs, 1H, NH).

ESI (+)MS: m/z 292 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea

m.p. 190-191°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 7.44 (s, 1H, H thiazole);

3.72 (s, 3H, CH₃); 6.61 (dd, 1H, J=2.4, 7.8, H-4'-phenyl);

6.94 (dd, 1H, J=2.0, 7.8, H-6'-phenyl); 7.13 (dd, 1H, J=2.0,

2.0, H-2'-phenyl); 7.20 (dd, 1H, J=7.8, 7.8, H-5'-phenyl);

8.95 (s, 1H, NH); 10.80 (s, 1H, NH).

ESI (+)MS: m/z 328 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8,

CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 7.03 (m, 2H, H-thiazole +

H-4'-phenyl); 7.29 (m, 2H, H-5', H-3'-phenyl); 7.43 (m, 2H,

H-2', H-6'-phenyl); 8.91 (s, 1H, NH); 10.30 (bs, 1H, NH).

ESI(+)-MS: m/z 262 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea

m.p. 191-193°C

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.16 (d, 6H, J=6.8,

CH₃CHCH₃); 3.00 (m, 1H, CH₃CHCH₃); 6.95 (d, 1H, J=1.0, H

thiazole); 7.40 (d, 2H, J=8.9 m-phenyl); 7.26 (d, 2H, J=8.9

o-phenyl); 9.01 (bs, 1H, NH); 10.40 (bs, 1H, NH).

ESI (+)MS: m/z 296 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-

urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;

5 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-
urea;

10 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea

5 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₂CHCH₃); 3.07 (m, 1H, CH₂CHCH₃); 7.07 (m, 2H, H-thiazole + H-4'-phenyl); 7.31 (dd, 1H, J=7.8, 7.8, H-5'-phenyl); 7.47 (d, 1H, J=7.8 H-3'-phenyl); 8.14 (d, 1H, J=7.8, H-6'-phenyl); 8.80 (bs, 1H, NH); 11.01 (bs, 1H, NH).

10 ESI (+)MS: m/z 296 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea
m.p. 210-212°C

20 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 7.29 (s, 1H, H-thiazole); 7.02 (ddd, 1H, J=1.6, 7.6, 7.6, H-4'-phenyl); 7.25 (ddd, 1H, J=1.6, 7.6, 7.6, H-5'-phenyl); 7.41 (dd, 1H, J=1.6, 7.6, H-3'-phenyl); 8.03 (dd, 1H, J=1.6, 7.6, H-6'-phenyl); 8.58 (s, 1H, NH); 11.31 (bs, 1H, NH).

25 ESI (+)MS: m/z 332 (100, (M+H)⁺);

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;

30 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

35 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-urea;

25 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;

40 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-

30 urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;

45 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-urea;

N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;

35 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea

50 m.p. 184-185°C;

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.7, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 3.85 (s, 3H, OCH₃); 6.92 (m, 1H, H-phenyl); 7.01 (m, 3H, H-phenyl + H-thiazole); 8.07 (d, 1H, J=8.3, H-6'-phenyl); 8.80 (bs, 1H, NH); 10.82 (s, 1H, NH).

ESI(+)-MS: m/z 292 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea
m.p. 218-220°C

¹H-NMR (300 MHz-DMSO-d₆) δ ppm: 3.79 (s, 3H, CH₃O); 6.90-7.98 (2m, 4H, phenyl); 7.36 (s, 1H, H thiazole); 8.57 (s, 1H, NH); 11.13 (bs, 1H, NH).

ESI (+)MS: m/z 328 (100, (M+H)⁺)

N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-urea;

N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;
N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.14 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H-thiazole); 7.74 (d, 2H, J=9.3, H-2', H-6'-phenyl); 8.18 (d, 2H, J=9.3, H-3', H-5'-phenyl); 9.65 (bs, 1H, NH); 11 (bs, 1H, NH).

ESI(+)-MS: m/z 307 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea
m.p. 220-222°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H thiazole); 7.56 (dd, 1H, J=8.2, 8.2, H-5'-phenyl); 7.77 (d, 1H, J=8.2, H-6'-phenyl); 7.83 (dd, 1H, J=8.2, 1.5, H-4'-phenyl); 8.58 (d, 1H, J=1.5, H-2'-phenyl); 9.45 (s, 1H, NH); 10.60 (bs, 1H, NH).

ESI (+)MS: m/z 307 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₂CHCH₃); 3.03 (m, 1H, CH₂CHCH₃); 4.31 (d, 2H, J=6.35, CH₂); 6.96 (m, 1H, NH-CH₂); 7.27 (m, 5H, phenyl).

ESI (+)MS: m/z 276 (100, (M+H)⁺);

N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;
 N-(5-bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;
 N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea;
 and
 N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-urea.

EXAMPLE 6

Preparation of a compound of formula (VI): 4-nitrophenyl-5-isopropyl-1,3-thiazol-2-ylcarbamate

To a solution of 4 g (28.13 mmol) of 5-isopropyl-2-amino-1,3-thiazole in 30 ml of anhydrous dichloromethane 5.7 g (28.13 mmol) of 4-nitrophenyl chloroformate were added dropwise at 0°C under nitrogen. Then 2.3 ml of pyridine

were added. The mixture was maintained at room temperature under stirring overnight and then filtered, giving 6.96 g (80% yield) of the title compound as a white solid.

m.p. 157-159°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 7.05 (s, 1H, H thiazole); 6.91 (d, 2H, J=9.2, H-3',5'-phenyl); 8.10 (d, 2H, J=9.2, H-2',6'-phenyl); 11.00 (bs, 1H, NH).
EI-MS: m/z 307 (0.5, M⁺); m/z 168 ((CH₃)₂-CH-thiazole-NCO)⁺; m/z 153 (100, (CH₃-CH-thiazole-NCO)⁺); m/z 139 (45, (OH-C₆H₄-NO₂)⁺).

EXAMPLE 7

Preparation of a compound of formula (I):N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-iodophenyl)urea

1 g (3.25 mmol) of 4-nitrophenyl-5-isopropyl-1,3-thiazol-2-ylcarbamate and 0.39 ml (3.25 mmol) of 3-iodoaniline were suspended under argon in 25 ml of acetonitrile. After 2 hours at 70°C the resulting solution was cooled, giving rise 0.923 g of the title compound, recrystallized from a mixture of diethylether/pentane 1/1.

m.p. 160-162°C

¹H-NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 7.03 (d, 1H, J=0.8, H thiazole); 7.07 (t, 1H, J=8.0, H-5'-phenyl); 7.35 (m, 2H, H-4',6'-phenyl); 8.00 (t, 1H, J=1.8, 1.8, H-2'-phenyl); 9.06 (bs, 1H, NH); 10.50 (bs, 1H, NH).
ESI(+)-MS: m/z 388 (100, (M+H)⁺).

By analogous procedure but employing 2-((2-propynylamino)methyl)benzenesulfonamide, 2-((((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)(2-propynylamino)methyl)benzenesulfonamide can be prepared.
m.p. 90-92°C

¹H-NMR (400 MHz-DMSO) δ ppm: 1.19 (d, 6H, J=6.8, CH₃CHCH₃); 2.93 (m, 1H, CH=C-); 3.13 (m, 1H, CH₃CHCH₃); 4.18, 5.08 (2m,

4H, $\text{CH}_2\text{Ph} + \text{CH}_2\text{C}\equiv\text{C}$); 6.89 (m, 1H, H-thiazole); 7.22 (m, 1H, H-3'-phenyl); 7.41, 7.53 (2m, 2H, H-5', H-4'-phenyl); 7.86 (m, 1H, H-6'-phenyl); 11.90 (bs, 1H, NH).

ESI(+)-MS: m/z 415 (100, (M+Na)⁺); m/z 393 (50, (M+H)⁺).

5 By analogous procedure but employing 1H-benzimidazol-6-amine, N-(1H-benzimidazol-5-yl)N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be obtained.

15 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.27 (d, 6H, J=6.8, CH_2CHCH_3); 3.09 (m, 1H, CH_2CHCH_3); 7.01 (s, 1H, H- thiazole);
10 7.13 (d, 1H, H-6'-benzimidazole); 7.49 (d, 1H, H-7'-benzimidazole); 7.81 (s, 1H, H-4'-benzimidazole); 8.03 (s, 1H, H-2'-benzimidazole).

ESI(+)-MS: m/z 302 (100, (M+H)⁺).

By analogous procedure but employing 1H-indole-6-amine, N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

25 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH_2CHCH_3); 3.06 (m, 1H, CH_2CHCH_3); 7.03 (bs, 1H, H thiazole);
30 6.33 (m, 1H, H-3'-indole); 6.84 (d, 1H, J=8.3, H-5'-indole);
20 7.23 (t, 1H, J=2.4, 2.4, H-2'-indole); 7.42 (d, 1H, J=8.3, H-4'-indole); 7.77 (s, 1H, H-7'-indole); 8.82 (s, 1H, NH); 10.18 (bs, 1H, NH); 10.95 (s, 1H, NH-indole).

ESI(+)-MS: m/z 301 (100, (M+H)⁺).

35 By analogous procedure but employing 1H-indole-5-amine, N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

40 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH_2CHCH_3); 3.06 (m, 1H, CH_2CHCH_3); 7.02 (s, 1H, H thiazole);
30 6.35 (m, 1H, H-3'-indole); 7.05 (dd, 1H, J=2.0, J=8.5, H-6'-indole); 7.30 (m, 2H, H-2', H-7'-indole); 7.67 (d, 1H, J=2.0, H-4'-indole); 8.68 (s, 1H, NH); 10.15 (s, 1H, NH); 10.98 (s, 1H, NH-indole).

ESI(+)-MS: m/z 301 (100, (M+H)⁺).

35

By analogous procedure but employing imidazo[1,2-a]pyridin-2-ylmethanamide, N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 4.40 (d, 2H, J=5.6, CH₂); 6.96 (d, 1H, J=1.2, H thiazole); 6.84 (dt, 1H, J=2.2, 6.8, H-6'-imidazopyridine); 7.20 (m, 1H, H-5'-imidazopyridine); 7.47 (m, 1H, H-7'-imidazopyridine); 7.78 (s, 1H, H-3'-imidazopyridine); 8.49 (m, 1H, H-4'-imidazopyridine); 7.01 (t, 1H, J=5.4, NH-CH₃); 10.23 (bs, 1H, NH-CO).

ESI(+)-MS: m/z 316 (100, (M+H)⁺); m/z 338 (85, (M+Na)⁺).

By analogous procedure but employing 1-methyl-2-[(2-aminophenoxy)methyl]1H-imidazole, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-{(1-methyl-1H-imidazol-2-yl)methoxy}phenyl)urea can be prepared.

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 3.70 (s, 3H, N-CH₃); 5.21 (s, 2H, CH₂); 6.92 (bs, 1H, H thiazole); 6.90-8.20 (m, 6H, imidazole+phenyl); 8.10 (bs, 1H, NH); 10.96 (s, 1H, NH).

ESI(+)-MS: m/z 372 (95, (M+H)⁺); m/z 410 (100, (M+K)⁺).

By analogous procedure but employing 2-(2-aminophenoxy)acetamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 4.50 (s, 2H, CH₂); 7.05 (d, 1H, J=1.0, H thiazole); 6.50-7.00 (m, 3H, phenyl); 8.10 (m, 1H, phenyl); 7.55 (s, 2H, NH₂); 8.67 (bs, 1H, NH); 10.86 (s, 1H, NH).

ESI(+)-MS: m/z 335 (50, (M+H)⁺); m/z 373 (100, (M+K)⁺).

By analogous procedure but employing (2S)-2-amino-2-phenylethanamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea can be prepared.

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=6.8, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 5.26 (d, 1H, J=7.7 CH₂); 6.95 (s, 1H, H-thiazole); 7.20-7.60 (m, 6H, NH-CH+phenyl); 7.20-7.80 (s, 2H, NH₂); 10.26 (bs, 1H, NH).

ESI(+)-MS: m/z 319 (25, (M+H)⁺); m/z 357 (100, (M+K)⁺);

By analogous procedure but employing (2R)-2-amino-2-phenylethanamide, N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=7.0, CH₂CHCH₃); 3.01 (m, 1H, CH₂CHCH₃); 5.26 (d, 1H, J=7.6 CH); 6.95 (d, 1H, J=1.3, H thiazole); 7.20-7.50 (m, 6H, NH-CH+phenyl); 7.21-7.79 (s, 2H, NH₂), 10.20 (bs, 1H, NH).

ESI(+)-MS: m/z 319 (100, (M+H)⁺); m/z 357 (65, (M+K)⁺).

By analogous procedure but employing 2-aminophenol, N-(2-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 204-206°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₂CHCH₃); 3.06 (m, 1H, CH₂CHCH₃); 7.02 (s, 1H, H-thiazole); 6.74 (m, 1H, H-5'-phenyl); 6.82 (m, 2H, H-3',H-4'-phenyl); 7.98 (d, 1H, J=7.6, H-6'-phenyl); 8.60 (bs, 1H, NH); 10.0 (bs, 1H, NH); 10.80 (bs, 1H, OH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

By analogous procedure but employing 3-aminophenol, N-(3-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 185-187°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₂CHCH₃); 3.05 (m, 1H, CH₂CHCH₃); 7.03 (m, 3H, H-thiazole + H-2',H-5'-phenyl); 6.39 (d, 2H, J=8.0, H-4'-phenyl); 6.77 (d, 2H, J=8.0, H-6'-phenyl); 8.81 (s, 1H, NH); 9.37 (s, 1H, NH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

By analogous procedure but employing 4-aminophenol, N-(4-hydroxyphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

m.p. 130-132°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₂CHCH₃); 3.05 (m, 1H, CH₂CHCH₃); 7.00 (s, 1H, H-thiazole); 6.68 (d, 2H, J=8.8, H-3', H-5'-phenyl); 7.21 (d, 2H, J=8.8, H-2',H-6'-phenyl); 8.60 (s, 1H, NH); 9.14 (s, 1H, NH); 10.18 (bs, 1H, OH).

ESI(+)-MS: m/z 278 (100, (M+H)⁺).

By analogous procedure but employing (2R)-2-amino-2-phenyl-1-ethanol, N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 3.60 (m, 2H, CH₂); 4.73 (m, 1H, CH); 5.00 (t, 1H, J=5.1, 5.1, OH); 6.95 (d, 1H, J=1.1, H thiazole); 7.10-7.40 (m, 6H, NH-CH+phenyl), 10.15 (s, 1H, NH).

ESI(+)-MS: m/z 306 (100, (M+H)⁺).

By analogous procedure but employing (2S)-2-amino-2-phenyl-1-ethanol, N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared.

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.19 (d, 6H, J=6.9, CH₃CHCH₃); 3.01 (m, 1H, CH₃CHCH₃); 3.59 (m, 2H, CH₂); 4.73 (m, 1H, CH); 5.02 (t, 1H, J=5.1, 5.1, OH); 6.95 (d, 1H, J=0.7, H thiazole); 7.20-7.40 (m, 6H, NH-CH+phenyl), 10.17 (s, 1H, NH).

ESI(+)-MS: m/z 306 (100, (M+H)⁺).

20

EXAMPLE 8

Preparation of a compound of formula (I): N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea

To a solution of 0.2 g (0.56 mmol) of N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-iodophenyl)urea in 3 ml of anhydrous N,N-dimethylformamide 0.6 ml of tetramethylguanidine, 0.088 ml (1.126 mmol) of D,L-1-butyn-3-ol, 19 mg (0.027 mmol) of bis(triphenylphosphine)palladium(II)dihydrochloride and 5.8 mg (0.03 mmol) of rameous iodide under argon were added successively. After 5 hours water was added and the mixture extracted with ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated, giving 0.116 g of the title compound as a yellowish solid. m.p. 71-73°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 1.37 (d, 3H, J=6.6, CH₃); 4.57 (m, 1H, CH); 5.43 (d, 1H, J=5.1, OH); 7.03 (s, 1H,

55

H thiazole); 7.02 (d, 1H, J=8.0, H-4'-phenyl); 7.27 (t, 1H, J=8.0, 8.0, H-5'-phenyl); 7.34 (d, 1H, J=8.0, H-6'-phenyl); 7.65 (s, 1H, H-2'-phenyl); 8.02 (s, 1H, NH); 10.40 (bs, 1H, NH).

ESI(+)-MS: m/z 330 (100, (M+H)⁺).

By analogous procedure and by starting from N,N-dimethyl-2-propyl-1-amine, N-(3-{3-(dimethylamino)-1-propynyl}phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 2.23 (s, 6H, N(CH₃)₂); 3.44 (s, 2H, CH₂); 7.03 (s, 1H, H-thiazole); 7.05 (d, 1H, J=7.8, H-4'-phenyl); 7.27 (t, 1H, J=7.8, 7.8, H-5'-phenyl); 7.36 (d, 1H, J=7.8, H-6'-phenyl); 7.64 (s, 1H, H-2'-phenyl); 9.04 (bs, 1H, NH); 10.45 (bs, 1H, NH).

ESI(+)-MS: m/z 343 (100, (M+H)⁺).

By analogous procedure and by starting from 3-methoxy-1-propyne, N-[3-(3-methoxy-1-propynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea can be prepared;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 3.32 (s, 3H, CH₃); 4.31 (s, 2H, CH₂); 7.03 (s, 1H, H-thiazole); 7.08 (d, 1H, J=8.3, H-4'-phenyl); 7.29 (t, 1H, J=8.3, 8.3, H-5'-phenyl); 7.39 (d, 1H, J=8.3, H-6'-phenyl); 7.67 (s, 1H, H-2'-phenyl); 9.03 (s, 1H, NH); 10.40 (bs, 1H, NH).

ESI(+)-MS: m/z 330 (100, (M+H)⁺).

EXAMPLE 9

Preparation of a compound of formula (I): N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-aminophenyl)urea

A mixture of 1.55 g (5.05 mmol) of (5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitrophenyl)urea prepared as described in example 5 and 0.98 g ((17.7 mmol) of iron dust with 2.02 ml (35.35 mmol) of glacial acetic acid in 50 ml of ethanol was stirred at reflux under argon atmosphere. After 5 hours 1.5 l of water was added and the product extracted with

ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was finally purified by chromatography on a silica gel column (chloroform/methanol 47/3) giving 0.84 g of the title compound as a white solid.

m.p. 113-115°C

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (m, 1H, CH₃CHCH₃); 5.07 (s, 2H, NH₂); 7.02 (s, 1H, H-thiazole); 6.20 (dd, 1H, J=2.0, 7.8, H-4'-phenyl); 6.52 (dd, 1H, J=1.5, 8.3, H-6'-phenyl); 6.76 (bs, 1H, H-2'-phenyl); 6.89 (t, 1H, J=8.3, 8.3, H-5'-phenyl); 8.61 (s, 1H, NH); 10.13 (bs, 1H, NH).

ESI(+)-MS: m/z 277 (100, (M+H)⁺).

By analogous procedure and by starting respectively from N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-nitrophenyl)urea and N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitrophenyl)urea, the following compounds can be prepared:

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-aminophenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-aminophenyl)urea;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.22 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 4.83 (s, 2H, NH₂); 6.99 (s, 1H, H-thiazole); 6.50 (d, 2H, J=8.7, H-3', H-5'-phenyl); 7.05 (d, 2H, J=8.7, H-2', H-6'-phenyl); 8.42 (s, 1H, NH); 10.09 (bs, 1H, NH).

ESI(+)-MS: m/z 277 (100, (M+H)⁺).

Again by analogous procedure, and by starting respectively from 6-nitro-1H-indole and from 6-nitro-1H-benzimidazole, 1H-indol-6-amine and 1H-benzimidazol-6-amine can be prepared.

EXAMPLE 10

Preparation of a compound of formula (I): N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)phenyl)methanesulfonamide]
0.2 g (0.724 mmol) of N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-aminophenyl)urea were dissolved in 10 ml of absolute

5 ethanol and 0.2 g (1.95mmol) of potassium hydrogen
carbonate and 124.3 mg (1.0855 mmol) of
methanesulfonylchloride were added successively. The
10 mixture was maintained at 80°C under argon for 7 hours and
5 then evaporated. The residue was partitioned between water
and dichloromethane. The organic layer was then dried over
sodium sulfate and afforded, after concentration and
cooling, 104 mg of the title compound as a white solid.
15 m.p. 246-248°C
10 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8,
CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 2.97 (s, 3H, CH₃); 7.03 (s,
1H, H-thiazole); 6.84 (d, 1H, J=6.8, H-6'-phenyl); 7.19 (m,
20 2H, H-4', H-5'-phenyl); 7.39 (s, 1H, H-2'-phenyl); 9.00 (s,
1H, NH); 9.72 (bs, 1H, NH); 10.18 (bs, 1H, NHSO₂).
15 ESI(+)-MS: m/z 355 (100, (M+H)⁺).

EXAMPLE 11

Preparation of a compound of formula (I):2-[3-([(5-isopropyl-1,3-thiazol-2-yl)amino]carbonyl)amino)anilino]acetamide

20 To a solution of 0.2 g (0.724 mmol) of N-(5-isopropyl-1,3-
thiazol-2-yl)-N'-(3-aminophenyl)urea in 2 ml of N,N-
dimethylformamide, 100 mg (0.724 mmol) of 2-bromoacetamide
and 108.6 mg (1.95 mmol) of potassium hydrogencarbonate
35 were added successively. The mixture was maintained 8 hours
at 40°C under argon, then poured into water and extracted
with dichloromethane. The organic layer was then washed
with brine, dried over sodium sulfate and concentrated to
40 give, after cooling, 160 mg of the title compound.
30 m.p. 133-135°C

45 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8,
CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 3.54 (d, 2H, J=5.4, CH₂);
7.02 (s, 1H, H-thiazole); 5.88 (m, 1H, NH-CH₂); 6.21 (d, 1H,
J=7.8, H-4'-phenyl); 6.65 (d, 1H, J=7.8, H-6'-phenyl); 6.69
35 (s, 1H, H-2'-phenyl); 6.98 (t, 1H, J=7.8, 7.8, H-5'-
phenyl); 8.71 (s, 1H, NH); 10.11 (s, 1H, NH); 7.08, 7.29
50 (s, 2H, NH₂).

ESI(+)-MS: m/z 334 (100, (M+H)⁺).

EXAMPLE 12

Preparation of (2R)-2-amino-2-phenylethanamide

3.025 g (15 mmol) of (2R)-2-amino-2-phenylethanoate hydrochloride were suspended in 45 ml of dioxane and 45 ml of aqueous ammonium hydrate were added. After 8 hours at room temperature under stirring the solvent was evaporated and the residue redissolved with chloroform and washed with water. The organic layer was concentrated to afford 1.7 g of the title compound as a white solid.

By analogous procedure and by starting from (2S)-2-amino-2-phenylethanoate, (2S)-2-amino-2-phenylethanamide can be prepared.

EXAMPLE 13

Preparation of 1-methyl-2-[(2-nitrophenoxy)methyl]-1H-imidazole

A solution of 1.92 g (11.97 mmol) of o-nitrophenol sodium salt, 3.8 g (35.9 mmol) of sodium carbonate, 2 g (11.97 mmol) of 1-methyl-2-chloromethylimidazole hydrochloride in 30 ml of N,N-dimethylformamide were heated at 50°C for 2 hours. The mixture was then poured into water and extracted with ethylacetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated, affording 1.17 g of the title compound, recrystallized from diethylether.

m.p. 172-174°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 3.67 (s, 3H, CH₃); 5.34 (s, 2H, OCH₂); 6.86 (s, 1H, H-4-imidazole); 7.13 (m, 1H, H-6-phenyl); 7.19 (s, 1H, H-5-imidazole); 7.60 (m, 1H, H-3-phenyl).

ESI(+)-MS: m/z 234 (100, (M+H)⁺).

By analogous procedure and by starting from 2-chloroacetamide, 2-(2-nitrophenoxy)acetamide can be prepared.

m.p. 190-192°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.65 (s, 2H, CH₂); 7.14 (ddd, 1H, J=1.0, 7.5, 7.9, H-4); 7.22 (dd, 1H, J=1.0, 8.7); H-6); 7.32, 7.47 (2bs, 2H, CONH₂); 7.64 (ddd, J=1.5, 7.5, 8.7, H-5); 7.90 (dd, 1H, J=1.5, 7.9, H-3).

ESI(+)-MS: m/z 197 (100, (M+H)⁺).

EXAMPLE 14

Preparation of 1-methyl-2-[(2-aminophenoxy)methyl]-1H-imidazole

A solution of 1.13 g of 1-methyl-2-[(2-nitrophenoxy)methyl]-1H-imidazole in 70 ml of methanol with 0.14 g of palladium on charcoal 10 % was hydrogenated at 50 psi for 6 hours at room temperature. The catalyst was then separated by filtration and the solvent evaporated. The residue was finally purified by chromatography on a silica gel column (eluent: chloroform-methanol 48/2) giving rise 0.856 g of the title compound as a red oil.

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 3.72 (s, 3H, CH₃); 3.80 (bs, 2H, NH₂); 5.15 (s, 2H, H-3 + H-4-phenyl); 6.81 (m, 1H, H-5-phenyl); 6.90 (s, 1H, H-4-imidazole); 7.02 (m, 2H, H-6-phenyl + H-5-imidazole).

ESI(+)-MS: m/z 204 (100, (M+H)⁺).

By analogous procedure and by starting from 2-(2-nitrophenoxy)acetamide, 2-(2-aminophenoxy)acetamide can be prepared.

m.p. 114-116°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.30 (s, 2H, CH₂CO); 5.03 (s, 2H, NH₂); 6.45 (m, 1H, H-5); 6.61 (m, 1H, H-3); 6.67 (m, 1H, H-4); 6.72 (m, 1H, H-6); 7.45 (s, 1H, CONH₂); 7.73 (s, 1H, CONH₂).

ESI(+)-MS: m/z 167 (100, (M+H)⁺).

EXAMPLE 15

Preparation of 2-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-isoindole-1,3(2H)-dione

4 g (0.024 mol) of 2-(chloromethyl)imidazo[1,2-a]pyridine were dissolved in 140 ml of N,N-dimethylformamide and 4.81 g (0.026 mol) of potassium ftalimide were added portionwise. The mixture was heated at 60°C for 20 hours. The precipitate was filtered, washed with water, diethylether and finally tetrahydrofuran, affording 4.8 g of the title compound.

m.p. 230-232°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 4.88 (s, 2H, CH₂); 6.82 (m, 1H, H-6-imidazopyridine); 7.17 (m, 1H, H-5-imidazopyridine); 7.44 (m, 1H, H-7-imidazopyridine); 7.88 (m, 4H, H-phenyl); 8.42 (m, 1H, H-4-imidazopyridine).
ESI(+)-MS: m/z 278 (100, (M+H)⁺).

EXAMPLE 16

Preparation of imidazo[1,2-a]pyridin-2-ylmethanamine

A solution of 1.37 g (4.94 mmol) of 2-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-isoindole-1,3(2H)-dione in 14 ml of hydrazine hydrate 98 % and 1 ml of ethanol. Was stirred at room temperature for an hour. The mixture was then poured into 25 ml of sodium hydroxide 35 % and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated to give 0.426 g of the title compound crystallized from diethylether.

m.p. 91-93°C

¹H-NMR (400 MHz-DMSO-d₆) δ ppm: 1.98 (bs, 2H, NH₂); 3.78 (s, 2H, CH₂); 6.80 (m, 1H, H-6); 7.15 (m, 1H, H-5); 7.41 (m, 1H, H-7); 7.73 (s, 1H, H-3); 8.46 (m, 1H, H-4).
ESI(+)-MS: m/z 148 (100, (M+H)⁺).

EXAMPLE 17

Preparation of the polymer supported compound (VIII)

A solution of 8.72 g (69.1 mmol) of 4-mercaptophenol in 20 ml of dry N,N-dimethylformamide was added dropwise to a solution of 7.76 g (69.1 mmol) of potassium t-butoxyde in 120 ml of the same solvent, under argon atmosphere, at 5°C, over a period of 20 minutes. 25 g (19.75 mmol) of the

5 Merrifield resin (VII) (Novabiochem loading 0.79 mmol/g)
was added to the solution and the temperature was kept to
60°C. The mixture was gently stirred at 60°C for 18 hours
and at 22°C for 24 hours. The resin was then filtered,
10 washed with N,N-dimethylformamide, dichloromethane,
methanol and evaporated. The loading of 4-mercaptophenol on
the resin was calculated from the percentage of sulfur
determined via microanalysis: S 2.64 %; loading 0.755 mmol
15 S/g. The presence of OH group was confirmed via DRIFTS
20 (broad strong band 3180-3520 nm).

EXAMPLE 18

Preparation of the polymer supported compound (IX)

20 7.98 g (39.6 mmol) of 4-nitrophenylchloroformate and 4.35
15 ml (39.6 mmol) of N-methylmorpholine were added to 24 g
(19.8 mmol) of the polymer supported compound (VIII)
25 swelled in 200 ml of dichloromethane under argon
atmosphere. The mixture was stirred at 22°C for 22 hours.
The obtained compound (IX) was filtered, washed with
20 dichloromethane, methanol and evaporated under vacuum. The
30 loading of 4-nitro-phenylchloroformate on the resin was
calculated from the percentage of sulfur determined via
microanalysis: S 2.34 %; loading 0.731 mmol S/g. The
disappearance of the OH band (broad strong band 3400 nm)
35 and the appearance of carbonate group were monitored via
25 DRIFTS (strong band 1785 nm).

EXAMPLE 19

Preparation of a polymer supported compounds (X)

40 30 A solution of 2-amino-5-isopropyl-1,3-thiazole (39.6 mmol)
in 12.5 ml of dichloromethane was added to the polymer
supported compound (IX) (19.8 mmol) swelled in 200 ml of
45 dichloromethane under argon atmosphere. The mixture was
stirred at 22°C for 22 hours. The obtained compound (X) was
35 filtered, washed with dichloromethane, methanol and
evaporated under vacuum. The loading of 2 amino-5-
50 isopropyl-1,3-thiazole on the resin was calculated from the
percentage of sulfur determined via microanalysis: S 4.21

5 %; loading 0.724 mmol S/g. The presence of carbamate group
was confirmed via DRIFTS (strong band 1742 nm).

EXAMPLE 20

5 Preparation via parallel synthesis of the compounds of
10 formula (I)

15 The amines (V) (0.236 mmol) and N,N-diisopropylethylamine
10 (0.236 mmol) were added to the polymer supported compounds
15 (X) (0.118 mmol) swelled in 3 ml of toluene in the Argonaut
20 Quest 210 apparatus vessels. 128 mg (4 eq) of N,N-
20 diisopropylethylamine resin bounded (PS-DIEA loading 3.68
25 mmol/g) was used whenever the amines were in the salified
30 form. The reactions were stirred for 22 hours at 60°C,
then the reaction mixtures were filtered and the resin
15 washed with dichloromethane. The liquid phase, recovered in
Climax test tubes, was evaporated under nitrogen flux at
25 35°C using Liebisch Termochem Metal-block thermostat. The
obtained crude products were triturated with diethylether-
dichloromethane and the resulting solids were filtered on
20 frit equipped syringes (Alltech extract-clean filter tubes
30 1.5 ml, Alltech Teflon frits for 1.5 ml tubes). The products
were finally dried under vacuum.

Employing this procedure and using the suitable amine the
following compounds can be prepared:

- 35 25 N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorophenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyanophenyl)urea;
40 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-cyanophenyl)urea;
30 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-
dimethylphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-fluorobenzyl)urea;
45 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-acetylphenyl)urea
¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0,
35 CH₃CHCH₃); 3.06 (m, 1H, CH₃CHCH₃); 2.55 (s, 3H, COCH₃); 7.32
(t, 1H, J=7.6, H-5'-phenyl); 7.44 (t, 1H, J=7.9, H-5'-
50 phenyl); 7.5-7.8 (m, 2H, H-4', H-6'-phenyl); 8.08 (s, 1H,

H-2'-phenyl); 7.04 (s, 1H, H-thiazole); 9.2 (bs, 1H, CONH-phenyl); 10.5 (bs, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-acetylphenyl)urea;

3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-isopropylphenyl)urea;

3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzamide

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₂CHCH₃); 3.05 (ept, 1H, J=6.8, CH₂CHCH₃); 7.32 (t, 1H, J=7.6, H-5'-phenyl); 7.35 (t, 1H, J=1.5, H-2'-phenyl); 7.49 (d, 1H, J=7.6, H-6'-phenyl); 7.62 (dd, 1H, J=7.6, 1.5, H-4'-phenyl); 7.04 (s, 1H, H-thiazole); 9.64 (s, 1H, CONH-phenyl); 10.36 (s, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-butylphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluoromethylphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-bromophenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-cyclohexylphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0, CH₂CHCH₃); 3.05 (m, 1H, CH₂CHCH₃); 6.96 (m, 4H, H-3', H-5'-phenyl, H-2', H-6'-phenoxy); 7.02 (s, 1H, H-thiazole); 7.08 (m, 1H, H-4'-phenoxy); 7.35 (m, 2H, H-3', H-5'-phenoxy); 7.47 (m, 2H, H-2', H-6'-phenyl); 8.95 (bs, 1H, CONH-phenyl); 10.3 (bs, 1H, NHCONH);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8, CH₂CHCH₃); 3.05 (ept, 1H, J=6.8, CH₂CHCH₃); 2.22 (s, 6H, 2 CH₃); 6.65-7.06 (m, 3H, H-phenyl); 7.02 (s, 1H, H-thiazole); 6.71 (s, 1H, H-phenyl); 6.72 (s, 1H, H-phenyl); 8.75 (bs, 1H, CONH-phenyl); 10.3 (bs, 1H, NHCONH).

ESI(+)-MS: m/z 362 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy[1,1'-biphenyl]-4-yl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-3,4-dihydro-2(1H)-isoquinoline carboxamide;

N-benzyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-methylurea;

N-(5-isopropyl-1,3-thiazol-2-yl)-6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinoline carboxamide

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.4, CH₃CHCH₃); 2.99 (ept, 1H, J=6.8, CH₃CHCH₃); 2.7 (t 2H, J=5.5, CH₂NCH₂CH₃); 3.68 (t, 2H, J=5.5, CH₂NCH₂CH₃); 3.69 (s, 3H, OCH₃); 3.71 (s, 3H, OCH₃); 4.55 (s, 2H, CH₂NCH₂CH₃); 6.97 (s, 1H, H-thiazole); 6.71 (s, 1H, H-phenyl); 6.72 (s, 1H, H-phenyl); 10.7 (bs, 1H, NH).

ESI(+)-MS: m/z 362 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)phenyl]urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-6-methyl)phenyl]urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=7.0, CH₃CHCH₃); 3.07 (m, 1H, J=7.0, CH₃CHCH₃); 3.68, 3.80 (two s 6H, 2-OCH₃); 7.04 (d, J=1.0, 1H, H-thiazole); 6.53 (dd, 1H, J=3.0, 8.9, H-4'-phenyl); 6.93 (d, 1H, J=8.9, H-3'-phenyl); 7.79 (d, 1H, J=3.0, H-6'-phenyl); 8.7 (bs, 1H, NHPh); 10.9 (bs, 1H, NHCONHPh);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=7.0, CH₃CHCH₃); 3.05 (ept, 1H, J=7.0, CH₃CHCH₃); 3.7 (s 3H, OCH₃); 3.73 (s, 3H, OCH₃); 7.02 (s, 1H, H-thiazole); 6.8-7.2 (m,

5 3H, H-phenyl); 8.76 (s, 1H, NHCONHPh); 10.2 (s, 1H, NHCONHPh);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-methoxy-5-chloro)phenyl]urea;
10 5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-4-methoxyphenyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;
15 N-[(1,1'-biphenyl)-2-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
10 N-ethyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-phenylurea;
N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-2-methoxyphenyl]acetamide;
20 2-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-N-phenylbenzamide;
15 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;
25 N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino]phenyl]-N-methyl acetamide
20 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.22 (d, 6H, J=6.6, CH₃CHCH₃); 3.08 (m, 1H, CH₃CHCH₃); 1.73 (s, 3H, NCOCH₃);
30 7.03 (s, 1H, H-thiazole); 3.09 (s, 3H, CH₃NCOCH₃); 7.23 (d, 2H, J=8.1, H-6', H-2'-phenyl); 7.51 (d, 2H, J=8.1, H-5', H-3'-phenyl); 9.1 (bs, 1H, NHCONHPh); 10.4 (bs, 1H, NHCONHPh);
35 25 N-(2-([cyclohexyl(methyl)amino]methyl)phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-[3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methoxyphenyl]acetamide;
40 N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;
30 N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea
45 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 2.99 (ept, 1H, J=6.8, CH₃CHCH₃); 4.32 (d, 2H, J=5.6, NHCH₂); 6.26 (d, 1H, J=3, H-5'-furyl); 6.4 (d, 1H, J=3, H-4'-furyl); 6.98 (s, 1H, H-thiazole); 6.93 (t, 1H, NHCH₂); 7.59 (s, 1H, H-3'-furyl); 10.19 (bs, 1H, NHCO).
50 ESI(+)-MS: m/z 266 (100, (M+H)⁺);

- 5 N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-methyl-1H-pyrrol-
2-yl)ethyl)urea;
- 10 5 N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-
yl)urea
1H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=7.0,
CH₃CHCH₃); 3.01 (ept, 1H, J=7.0, CH₃CHCH₃); 3.69 (s, 3H,
15 OCH₃); 3.72 (s, 3H, OCH₃); 4.22 (d, 2H, J=5.0, NHCH₂Ph); 6.8-
10 6.9 (m, 3H, H-phenyl); 6.96 (s, 1H, H-thiazole);
N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-
triazaspiro[4.5]decane-8-carboxamide
20 1H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=6.8,
CH₃CHCH₃); 3.03 (ept, 1H, J=6.8, CH₃CHCH₃); 1.62 (d, 2H,
15 J=13.6, H-3'eq, H-5'eq-piperidine); 2.4 (td, 2H, J=13.6,
5.1, H-3'ax, H-5'ax-piperidine); 3.46 (bt, 2H, J=10.4, H-
25 6'ax, H-2'ax-piperidine); 4.14 (bd, 2H, J=10.4, H-6'eq, H-
2'eq-piperidine); 4.58 (s, 2H, CONHCH₂NPh); 6.6-6.7 (m, 3H,
H-2', H-6', H-4'-phenyl); 7.14 (t, 2H, J=7.5, H-3', H-5'-
20 phenyl); 6.98 (bs, 1H, H-thiazole); 8.75 (bs, 1H,
CONHCH₂NPh); 10.85 (bs, 1H, thiazole-NHCON);
N-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxo-8-
azaspiro[4.5]decane-8-carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-
35 piperidinyl)ethyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-(1-
morpholinyl)ethyl)urea;
4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-
40 piperazine carboxamide;
30 N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-
1,3-thiazol-2-yl)urea;
4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-
45 thiazol-2-yl)-1-piperidine carboxamide;
N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-
yl)urea;
- 50
- 55

- 5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;
N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 5 N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
N-(4-[ethyl(isopropyl)amino]phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 10 N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-1-phenyl-1H-pyrazole-4-carboxamide;
- 20 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
- 15 n-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;
- 25 N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide
¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.23 (d, 6H, J=7.0, CH₃CHCH₃); 3.01 (ept, 1H, J=7.0, CH₃CHCH₃); 1.69 (bd, 2H, J=9.8, H-3'eq, H-5'eq-piperidine); 2.21 (m, 2H, H-3'ax, H-5'ax-piperidine); 3.46 (bt, 2H, J=12.4, H-2'ax, H-6'ax-piperidine); 4.14 (m, 3H, H-2'eq, H-6'eq, H-4'ax-piperidine); 6.9-7.2 (m, 4H, aromatics); 6.98 (s, 1H, H-thiazole);
- 30 10.8 (bs, 2H, NHCONH);
N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea
- 35 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.05 (ept, 1H, J=6.8, CH₃CHCH₃); 7.5 (dd, 1H, J=8.8, 1.9, H-5'-benzothiazole); 7.98 (d, 1H, J=8.8, H-4'-benzothiazole); 8.38 (d, 1H, J=1.9, H-7'-benzothiazole); 9.22 (s, 2H, H-2'-benzothiazole + NHCONHPh); 7.04 (s, 1H, H-thiazole); 10.41 (s, 1H, NHCONHPh);
- 40 N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 35 N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 50

- 5 N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine
carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-
10 dihydro-1H-indol-5-yl)urea;
5 N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine
carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine
15 carboxamide;
4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine
10 carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-
3-carboxamide;
20 N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-
piperazine carboxamide
15 ¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=7.0,
CH₂CHCH₃); 2.99 (ept, 1H, J=7.0, CH₂CHCH₃); 2.44 (s, 3H,
25 CH₃COPh); 3.29 (bt, 4H, CH₂-2', 6'-piperazine); 3.63 (bt, 4H,
CH₂-3', 5'-piperazine); 6.97 (d, 2H, J=9.2, H-3', 5'-
phenyl); 7.8 (d, 2H, J=9.2, H-2', 6'-phenyl); 6.97 (s, 1H,
20 H-thiazole); 10.95 (bs, 1H, NHCON);
30 4-[bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-
piperazine carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-
1H-1,5-benzodiazepine-1-carboxamide;
35 25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-
naphtalenyl)urea;
N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-
yl)urea;
40 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-
30 piperidine carboxamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-
benzofuran-5-yl)urea;
45 N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-
piperazine carboxamide;
35 N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-
quinoxaline;
50 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₃CHCH₃); 3.07 (m, 1H, CH₃CHCH₃); 6.94 (d, 1H, J=8.4, H-5'-indazole); 7.65 (d, 1H, J=8.4, H-4'-indazole); 7.94 (m, 2H, H-3', H-7'-indazole); 7.04 (s, 1H, H-thiazole); 9.12 (bs, 1H, CONH-indazole); 10.30 (bs, 1H, NH-thiazole); 12.87 (bs, 1H, NH-indazole).
ESI(+)-MS: m/z 302 (100, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.9, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.38 (d, 2H, J=5.9, CH₂); 7.3-7.44 (m, 4H, phenyl); 6.97 (d, 1H, J=0.9, H-thiazole); 7.10 (bs, 1H, NHCH₃); 10.32 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 310 (100, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.32 (d, 2H, J=6.1, CH₂); 6.97 (d, 1H, J=0.9, H-thiazole); 7.0-7.4 (m, 5H, phenyl + NHCH₃); 10.30 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 294 (100, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.7, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.30 (d, 2H, J=6.1, CH₂); 7.28 (dd, 1H, J=2.0, 8.2, H-6'-phenyl); 7.52 (d, 1H, J=2.0, H-2'-phenyl); 7.58 (d, 1H, J=8.2, H-5'-phenyl); 6.97 (d, 1H, J=0.9, H-thiazole); 7.12 (bs, 1H, NHCH₃); 10.41 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 143 (100, isopropylaminothiazole+H)⁺; m/z 344 (65, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.7, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.30 (d, 2H, J=6.0, CH₂); 6.97 (d, 1H, J=0.9, H-thiazole); 7.0-7.4 (m, 4H, phenyl + NHCH₃); 10.20 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 312 (100, (M+H)⁺);

5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea
1H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.9 CH₃CHCH₃);
3.02 (m, 1H, CH₃CHCH₃); 4.35 (d, 2H, J=5.8, CH₂); 7.08 (m,
10 2H, H-3', H-5'-phenyl); 7.39 (m, 1H, H-4'-phenyl); 6.95 (d,
5 1H, J=0.9, H-thiazole); 7.04 (bs, 1H, NHCH₃); 10.08 (bs, 1H,
NH-thiazole).
ESI(+)-MS: m/z 312 (100, (M+H)⁺);
15 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-
10 methoxy)benzyl]urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-furyl)urea
1H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8,
20 CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 2.21 (s, 3H, CH₃); 4.23 (d,
2H, J=5.8, CH₂); 5.97, 6.11 (2s, 2H, furane); 6.96 (d, 1H,
15 J=1.0, H-thiazole); 6.91 (bs, 1H, NHCH₃); 10.14 (bs, 1H, NH-
thiazole).
ESI(+)-MS: m/z 280 (100, (M+H)⁺);
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
methylsulfonylbenzyl)urea;
20 N-[(1R, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-
isopropyl-1,3-thiazol-2-yl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea
1H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8,
35 CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.29 (d, 2H, J=6.1, CH₂);
25 7.3, 7.37 (2d, 4H, J=8.5, phenyl); 6.97 (d, 1H, J=0.9, H-
thiazole); 7.06 (bs, 1H, NHCH₃); 10.30 (bs, 1H, NH-
thiazole).
ESI(+)-MS: m/z 310 (100, (M+H)⁺);
40 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
30 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-
dimethoxybenzyl)urea
1H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8,
45 CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.24 (d, 2H, J=5.9, CH₂);
3.71 (s, 6H, 2 OCH₃); 6.37 (s, 1H, H-4'-phenyl); 6.44 (s,
35 2H, H-2', H-6'-phenyl); 6.97 (s, 1H, H-thiazole); 6.99 (bs,
50 1H, NHCH₃); 10.22 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 336 (100, (M+H)⁺);

5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-
10 trimethoxybenzyl)urea

5 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.24 (d, 2H, J=5.9, CH₂); 3.60, 3.65 (3s, 9H, 3 OCH₃); 6.60 (s, 2H, phenyl); 6.97 (s, 1H, H-thiazole); 6.99 (bs, 1H, NHCH₃); 10.20 (bs, 1H, NH-thiazole).

10 ESI(+)-MS: m/z 366 (100, (M+H)⁺); m/z 181 (100, (CH₃O)₃-C₆H₂)⁺;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea

15 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.24 (d, 2H, J=5.9, CH₂); 3.70, 3.78 (2s, 6H, 2 OCH₃); 6.48 (dd, 1H, H-5'-phenyl); 6.52 (d, 1H, H-3'-phenyl); 7.05 (d, 1H, H-6'-phenyl); 6.97 (s, 1H, H-thiazole); 6.80 (bs, 1H, NHCH₃); 10.10 (bs, 1H, NH-thiazole).

20 ESI(+)-MS: m/z 336 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;

25 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R, 2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;

30 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;

45 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;

35 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinoliny)urea

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¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₂CHCH₃); 3.07 (m, 1H, CH₂CHCH₃); 2.61 (s, 3H, CH₃); 7.05 (s, 1H, H-thiazole); 7.36 (d, 1H, J=8.4, H-3'-quinoline); 7.65 (dd, 1H, J=2.0, 9.0, H-7'-quinoline); 7.85 (d, 1H, J=9.0, H-8'-quinoline); 8.14 (m, 2H, H-4', H-5'-quinoline); 9.22 (bs, 1H, NHCONH-quinoline); 10.40 (bs, 1H, NH-thiazole).
ESI(+)-MS: m/z 185 (100, (MH-(CH₂)₂-CH-amino-thiazole)⁺); 327 (75, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.9, CH₂CHCH₃); 3.05 (m, 1H, CH₂CHCH₃); 7.03 (s, 1H, H-thiazole); 3.94 (s, 2H, CH₂); 7.27 (d, 2H, H-3', H-5'-phenyl); 7.48 (d, 2H, J=8.5, H-2', H-6'-phenyl); 9.01 (bs, 1H, NH-phenyl); 10.30 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 301 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.27 (d, 6H, J=6.8, CH₂CHCH₃); 3.13 (m, 1H, CH₂CHCH₃); 7.17 (s, 1H, H-thiazole); 7.44 (m, 1H, H-3'-quinoline); 7.50 (m, 1H, H-6'-quinoline); 7.75 (m, 1H, H-7'-quinoline); 7.82 (m, 1H, H-8'-quinoline); 7.90 (m, 1H, H-5'-quinoline); 8.34 (m, 1H, H-4'-quinoline); 10.45 (bs, 1H, NHCONH-quinoline); 13.02 (bs, 1H, NHCON).

ESI(+)-MS: m/z 313 (100, (M+H)⁺).

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₂CHCH₃); 3.06 (m, 1H, CH₂CHCH₃); 7.04 (s, 1H, H-thiazole); 5.35 (s, 1H, CH₂); 7.58 (d, 1H, J=8.4, H-5'-phenyl); 7.71 (d, 1H, J=8.4, H-6'-phenyl); 8.08 (s, 1H, H-2'-phenyl); 9.34 (bs, 1H, NHCONHPh); 10.50 (bs, 1H, NHCON).

ESI(+)-MS: m/z 318 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)urea;

methyl-3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methylbenzoate

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.25 (d, 6H, J=6.8, CH₃CHCH₃); 3.10 (m, 1H, CH₃CHCH₃); 2.30 (s, 3H, CH₃-phenyl); 3.80 (s, 3H, CH₃O); 7.05 (s, 1H, H-thiazole); 7.30 (d, 1H, H-5'-phenyl); 7.58 (dd, 1H, H-6'-phenyl); 8.55 (m, 2H, H-2'-phenyl + NHPh); 10.80 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 334 (100, (M+H)⁺);

methyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-3-methylbenzoate

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 2.25 (s, 3H, CH₃-phenyl); 3.83 (s, 3H, CH₃O); 7.03 (s, 1H, H-thiazole); 7.30 (d, 1H, H-3'-phenyl); 7.53 (dd, 1H, H-4'-phenyl); 8.50 (m, 2H, H-6'-phenyl + NHPh); 10.70 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 334 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.03 (s, 1H, H-thiazole); 6.84, 7.20 (2m, 2H, H-5', H-6''imidazopyridine); 7.50, 7.90 (2m, 5H, H-2', H-3', H-5', H-6'-phenyl + H-7'-imidazopyridine); 8.30 (s, 1H, H-3'-imidazopyridine); 8.50 (d, 1H, H-4'-imidazopyridine); 9.00 (bs, 1H, NHCONHPh); 10.30 (bs, 1H, NHCON).

ESI(+)-MS: m/z 236 (100, (MH-(CH₃)₂-CH-amino-thiazole)⁺); m/z 378 (85, (M+H)⁺);

ethyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoate

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.00 (s, 1H, H-thiazole); 1.15 (t, 3H,

CH₃); 3.58 (s, 2H, CH₂-phenyl); 4.06 (q, 2H, CH₂O); 7.16, 7.38 (2d, 4H, phenyl); 8.90 (bs, 1H, NHCONHPh); 10.30 (bs, 1H, NHCON).

ESI(+)-MS: m/z 348 (100, (M+H)⁺);

(2R)-1-benzyl-2-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)propanamide;
2-hydroxy-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)benzoic acid

2-chloro-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;

¹H- NMR (400 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.04 (m, 1H, CH₃CHCH₃); 7.02 (s, 1H, H-thiazole); 7.35 (d, 1H, J=8.8, H-5'-phenyl); 7.55 (dd, 1H, H-6'-phenyl); 7.88 (bs, 1H, H-2'-phenyl); 9.75 (bs, 1H, NHCONHPh); 11.00 (bs, 1H, NHCON).

ESI(+)-MS: m/z 340 (100, (M+H)⁺);

3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid

¹H- NMR (500 MHz-DMSO-d₆) δ ppm: 1.24 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 7.04 (s, 1H, H-thiazole); 7.40 (dd, 1H, J=7.9, H-5'-phenyl); 7.58, 7.63 (2d, 2H, J=7.9, H-4', H-6'-phenyl); 8.13 (s, 1H, H-2'-phenyl); 9.28 (s, 1H, NHCONHPh); 10.50 (bs, 1H, NHCON).

ESI(+)-MS: m/z 306 (100, (M+H)⁺);

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;

N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea

¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.21 (d, 6H, J=6.8, CH₃CHCH₃); 3.03 (m, 1H, CH₃CHCH₃); 4.32 (d, 2H, J=6.1, CH₂); 3.72, 3.75 (2s, 6H, 2 OCH₃); 6.8-7.0 (m, 3H, phenyl); 6.97

(s, 1H, H-thiazole); 6.90 (bs, 1H, NHCH₃); 10.20 (bs, 1H, NH-thiazole).

ESI(+)-MS: m/z 336 (100, (M+H)⁺);

5 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;

10 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;

15 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea

10 ¹H- NMR (300 MHz-DMSO-d₆) δ ppm: 1.20 (d, 6H, CH₃CHCH₃); 3.00 (m, 1H, CH₃CHCH₃); 0.85 (t, 3H, CH₃); 1.20-1.40 (m, 4H, CH₂-CH₃); 3.10 (m, 2H, CH₂-NH); 6.94 (d, 1H, J=1.0, H-thiazole); 6.49 (t, 1H, NHCH₃); 10.5 (bs, 1H, NH-thiazole).

20 ESI(+)-MS: m/z 242 (100, (M+H)⁺);

15 N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;

25 N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;

N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;

N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;

N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;

20 N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;

30 N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;

N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;

N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-thiazol-2-yl)urea;

35 25 N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-3-yl)urea;

N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;

40 N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

30

All compounds were characterized by mass spectrometry (MS).

45 LC-MS confirmed that in each case the principle component

had a molecular ion corresponding to the expected product.

The compounds showed an HPLC area % ranging from 70 to 100.

35 HPLC analysis:

50 Instrument: Beckman System Gold Chromatographer (127 Solvent module, 168 Detector, 507e Autosampler)

Mobile A: H₂O/CH₃CN (90/10) + 0.1 % TFA.

Mobile B: H₂O/CH₃CN (10/90) + 0.075 % TFA.

Flow rate: 1.5 ml/min.

Sample volume: 20 cml.

5 Column: Supelco™, Discovery RP Amide C16, 5µm, (50x4.6)mm

Temp: 25°C.

Gradient:

Time (min)	% A	% B
0	0	100
6.5	0	100
7	100	0
10	100	0

10 Detection: diode array UV 254 nm.

25 All the compounds were analyzed by MS spectrometry (ESI)
using a LCQ Finnigan Mass Spectrometer.

37 randomly chosen compounds were analyzed by H¹-NMR.

The spectra were run on a Varian XL 400 Spectrometer.

Claims

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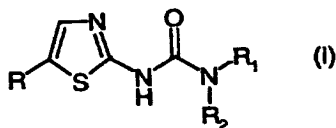
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CLAIMS

1. The use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) C₃-C₆ cycloalkyl;
- iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

- i) straight or branched C₁-C₆ alkyl;
- ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;
- iii) aryl or arylcarbonyl;
- iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₆ alkyl or C₃-C₆ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R₁ and R₂ form a substituted or unsubstituted group selected

from:

- i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or
- ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

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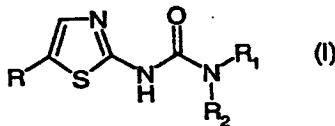
2. Use according to claim 1 wherein the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

3. Use according to claim 2 wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. Use according to claim 1 wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. Use according to any one of the preceding claims wherein the medicament enables tumor angiogenesis and metastasis inhibition.

6. A compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



wherein

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ISA/EP

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R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C₁-C₆ alkyl;

ii) C₆-C₁₀ cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₁ is an optionally further substituted group selected from:

i) straight or branched C₁-C₆ alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R₂ is hydrogen, a straight or branched C₁-C₆ alkyl or C₆-C₁₀ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R₁ and R₂ form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

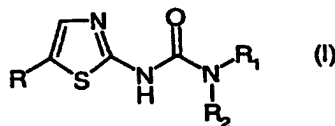
for use as a medicament; provided that:

a) when R is a chlorine atom and R₁ is hydrogen, then R₂ is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R₁ is hydrogen, then R₂ is not 4-(5-oxazolyl)phenyl.

30

7. A compound which is a 2-amino-1,3-thiazole derivative of formula (I)



wherein

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5 R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

10 i) straight or branched C₁-C₆ alkyl;

5 ii) C₃-C₆ cycloalkyl;

10 iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

15 R₁ is an optionally further substituted group selected from:

10 i) straight or branched C₁-C₆ alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

20 iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

15 R₂ is hydrogen, a straight or branched C₁-C₆ alkyl or C₁-C₆ alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

25 R₁ and R₂ form a substituted or unsubstituted group selected from:

30 i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof; provided that:

35 25 a) when R is chlorine or bromine and R₂ is hydrogen, then R₁ is not unsubstituted C₁-C₆ alkyl, phenyl, trifluoromethylphenyl or an optionally substituted phenylcarbonyl;

40 b) when R is methyl and R₂ is hydrogen, then R₁ is not methyl, phenyl or 4-(5-oxazolyl)phenyl;

30 c) when R is nitrophenyl and R₂ is hydrogen, then R₁ is not haloalkyl;

45 d) when R is bromine or chlorine, then R₁ and R₂ are not both methyl groups.

35

50 8. A compound of formula (I) according to claim 7 wherein R is a halogen atom, a straight or branched C₁-C₆ alkyl group, a phenyl or a cycloalkyl group; R₂ is hydrogen and R₁

is an optionally substituted group selected from alkyl, aryl or arylalkyl.

9. A compound of formula (I) according to claim 8 wherein R is bromine or chlorine, a straight or branched C₁-C₄ alkyl group, a phenyl or a cycloalkyl group; R₁ is hydrogen and R₂ is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.

10. A compound of formula (I) according to claim 7 wherein R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C₁-C₄ cycloalkyl, straight or branched C₁-C₄ alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxyalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxyalkyl, carboxy, aryl optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxyalkyl or carboxy, or R is an aryl group optionally substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxyalkyl or carboxy; R₁ is a straight or branched C₁-C₄ alkyl group or an aryl group, each optionally substituted as above reported for R; R₂ is a hydrogen atom; and pharmaceutically acceptable salts thereof; provided that:

- 5 a) when R is chlorine or bromine then R₁ is not
unsubstituted C₁-C₄ alkyl, phenyl, trifluoromethylphenyl
or an optionally substituted phenylcarbonyl;
10 b) when R is methyl then R₁ is not methyl, phenyl or 4-(5-
5 oxazolyl)phenyl;
c) when R is nitrophenyl then R₁ is not haloalkyl.

15 11. A compound of formula (I) according to claim 7 wherein
R is a straight or branched C₁-C₄ alkyl group and, together
10 with the nitrogen atom to which they are bonded, R₁ and R₂
form a substituted or unsubstituted, optionally
benzocondensed or bridged 5 to 7 membered heterocycle, or a
20 9 to 11 membered spiro-heterocycle.

15 12. A compound of formula (I) according to claim 7 wherein
R is a straight or branched C₁-C₄ alkyl group; R₁ is a
25 straight or branched C₁-C₄ alkyl or C₁-C₄ alkenyl or alkynyl
group and R₂ is an aryl or arylalkyl group with from 1 to 4
carbon atoms within the straight or branched alkyl chain.

20 13. A compound of formula (I) according to any one of the
preceding claims, whenever appropriate in the form of
30 pharmaceutically acceptable salts, selected from the group
consisting of:

- 35 25 1) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
2) N-(5-bromo-1,3-thiazol-2-yl)-N'-phenyl-urea;
3) N-(5-phenyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
4) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-phenyl-urea;
40 5) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-
30 urea;
6) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-
urea;
45 7) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-phenyl)-
urea;
35 8) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-sulfamoyl-
phenyl)-urea;
50 9) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-
urea;

- 5 10) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-
urea;
11) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-methoxy-phenyl)-
urea;
10 5 12) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy-
phenyl)-urea;
13) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-
urea;
15 14) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-urea;
10 15) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-chloro-phenyl)-
urea;
16) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-chloro-
20 phenyl)-urea;
17) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-
15 urea;
18) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-urea;
25 19) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-chloro-phenyl)-
urea;
20) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-chloro-
20 phenyl)-urea;
21) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
30 urea;
22) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-urea;
23) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-chloro-phenyl)-
35 urea;
25 24) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-chloro-
phenyl)-urea;
25) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
40 26) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
urea;
27) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-methoxy-phenyl)-
45 urea;
28) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-methoxy-
35 phenyl)-urea;
29) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
50 urea;

- 5 30) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
- 31) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-phenyl)-
urea;
- 10 5 32) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-hydroxy-
phenyl)-urea;
- 33) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
- 15 34) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
- 10 35) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-phenyl)-
urea;
- 20 36) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-hydroxy-
phenyl)-urea;
- 15 37) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 25 38) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 39) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-methoxy-phenyl)-
urea;
- 20 40) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-methoxy-
phenyl)-urea;
- 30 41) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 35 25 42) N-(5-bromo-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 43) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-phenyl)-
urea;
- 40 44) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(2-hydroxy-
phenyl)-urea;
- 30 45) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 45 46) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 47) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-urea;
- 35 48) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-nitro-phenyl)-
urea;
- 50 49) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;

- 5 50) N-(5-bromo-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
51) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-urea;
52) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(4-amino-phenyl)-
urea;
10 5 53) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
urea;
54) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
55) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-urea;
15 56) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-nitro-phenyl)-
10 urea;
57) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
20 58) N-(5-bromo-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
59) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-urea;
15 60) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(3-amino-phenyl)-
urea;
25 61) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
62) N-(5-bromo-1,3-thiazol-2-yl)-N'-benzyl-urea;
63) N-(5-phenyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
20 64) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-benzyl-urea;
30 65) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
66) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
67) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-urea;
68) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-3-yl)-
35 25 urea;
69) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
70) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
71) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-urea;
40 72) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-4-yl)-
30 urea;
73) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
74) N-(5-bromo-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
45 75) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-urea;
76) N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-(pyrid-2-yl)-
35 urea;
77) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-
50 yl)-urea;

- 5 78) N-(5-bromo-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea;
- 79) N-(5-phenyl-1,3-thiazol-2-yl)-N'-(benzothiophen-2-yl)-
urea; N-(5-cyclopropyl-1,3-thiazol-2-yl)-N'-
10 5 (benzothiophen-2-yl)-urea;
- 80) N-(5-isopropyl-1,3-thiazol-2-yl)-4-morpholine
carboxamide;
- 81) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
15 methylphenyl)urea;
- 10 82) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
fluorophenyl)urea;
- 83) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
20 cyanophenyl)urea;
- 84) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
15 cyanophenyl)urea;
- 85) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-
25 dimethylphenyl)urea;
- 86) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
fluorobenzyl)urea;
- 20 87) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-
30 acetylphenyl)urea;
- 88) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
acetylphenyl)urea;
- 89) 3-(((5-isopropyl-1,3-thiazol-2-
35 yl)amino)carbonyl)amino)benzoic acid;
- 25 90) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
isopropylphenyl)urea;
- 91) 3-(((5-isopropyl-1,3-thiazol-2-
40 yl)amino)carbonyl)amino)benzamide;
- 30 92) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
methoxybenzyl)urea;
- 93) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
45 butylphenyl)urea;
- 94) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
35 trifluoromethylphenyl)urea;
- 95) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-bromophenyl)urea;
- 50 96) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-
cyclohexylphenyl)urea;

- 5 97) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-phenoxyphenyl)urea;
98) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-benzyloxyphenyl)urea;
10 5 99) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethylphenyl)urea;
100) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethylphenyl)urea;
15 101) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-methoxy[1,1'-biphenyl]-4-yl)urea;
10 102) N-(5-isopropyl-1,3-thiazol-2-yl)-3,4-dihydro-2(1H)-isoquinoline carboxamide;
20 103) N-benzyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-methylurea;
15 104) N-(5-isopropyl-1,3-thiazol-2-yl)-6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinoline carboxamide;
25 105) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-4-methyl)-phenyl]urea;
106) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-chloro-6-methyl)phenyl]urea;
30 20 107) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxyphenyl)urea;
108) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
35 25 109) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-methoxy-5-chloro)phenyl]urea;
110) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-4-methoxyphenyl)urea;
40 111) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dichlorophenyl)urea;
30 112) N-[(1,1'-biphenyl)-2-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
45 113) N-ethyl-N'-(5-isopropyl-1,3-thiazol-2-yl)-N-phenylurea;
114) N-[4-({(5-isopropyl-1,3-thiazol-2-yl)amino}carbonyl)amino)-2-methoxyphenyl]acetamide;
35 115) 2-({(5-isopropyl-1,3-thiazol-2-yl)amino}carbonyl)amino)-N-phenylbenzamide;
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- 5 116) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-morpholinophenyl)urea;
- 117) N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino]phenyl]-N-methyl acetamide;
- 10 118) N-(2-((cyclohexyl(methyl)amino)methyl)phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 119) N-[3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino]-4-methoxyphenyl]acetamide;
- 15 120) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-methoxyphenyl)-1-piperazine carboxamide;
- 10 121) N-(2-furylmethyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 20 122) N-(4-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 123) N-(2-methoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 25 124) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;
- 125) N-(3,4-dimethoxybenzyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 30 126) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
- 127) n-(5-isopropyl-1,3-thiazol-2-yl)-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide;
- 35 128) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-piperidinyl)ethyl]urea;
- 129) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[2-(1-morpholinyl)ethyl]urea;
- 40 130) 4-(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 30 131) N-[4-(4-chlorophenyl)-3-ethyl-5-isoxazolyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 45 132) 4-[(4-fluorophenyl)(hydroxy)methyl]-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 35 133) N-(3-ethynylphenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 50 134) N-(2-methoxy-3-fluorophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;

- 5 135) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-oxo-1-piperidinyl)urea;
- 10 136) N-(3-acetylaminophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 137) N-[3-(2-furyl)-1H-pyrazol-5-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 138) N-(4-[ethyl(isopropyl)amino]phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 15 139) N-(1,3-benzodioxol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 140) 5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-1-phenyl-1H-pyrazole-4-carboxamide;
- 20 141) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-pyridinylmethyl)urea;
- 15 142) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyrazinyl)urea;
- 25 143) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-phenyl-1,3,4-oxadiazol-2-yl)urea;
- 144) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine carboxamide;
- 30 145) N-(1,3-benzothiazol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 146) N-(1,3-dimethyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 35 25 147) N-(3-phenyl-1-methyl-1H-pyrazol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 148) N-(5-isopropyl-1,3-thiazol-2-yl)-3-hydroxy-1-piperidine carboxamide;
- 40 149) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea;
- 30 150) N-(5-isopropyl-1,3-thiazol-2-yl)-4-benzyl-1-piperazine carboxamide;
- 45 151) N-(5-isopropyl-1,3-thiazol-2-yl)-4-methyl-1-piperazine carboxamide;
- 35 152) 4-hydroxy-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 50 153) N-(5-isopropyl-1,3-thiazol-2-yl)-3-azabicyclo[3.2.2]nonane-3-carboxamide;
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- 5 154) N-(5-isopropyl-1,3-thiazol-2-yl)-4-(4-acetylphenyl)-1-piperazine carboxamide;
- 155) 4-{bis(4-fluorophenyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperazine carboxamide;
- 10 5 156) N-(5-isopropyl-1,3-thiazol-2-yl)-4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide;
- 157) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5,6,7,8-tetrahydro-1-naphtalenyl)urea;
- 15 158) N-(4-phenyl-2-thiazolyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 10 159) 4-(4-fluorobenzoyl)-N-(5-isopropyl-1,3-thiazol-2-yl)-1-piperidine carboxamide;
- 20 160) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-1,3-dihydro-2-benzofuran-5-yl)urea;
- 15 161) N-(5-isopropyl-1,3-thiazol-2-yl)-4'-(2-pyrimidinyl)-1-piperazine carboxamide;
- 25 162) N-(5-isopropyl-1,3-thiazol-2-yl)-3-oxo-3,4-dihydro-1(2H)-quinoxaline;
- 163) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-indazol-6-yl)urea;
- 20 164) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-chlorobenzyl)urea;
- 30 165) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dichlorobenzyl)urea;
- 35 25 166) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-fluorobenzyl)urea;
- 167) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-dichlorobenzyl)urea;
- 40 168) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-difluorobenzyl)urea;
- 30 169) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-difluorobenzyl)urea;
- 45 170) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-2,6-difluorobenzyl)urea;
- 35 171) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(4-hydroxy-3-methoxy)benzyl]urea;
- 50 172) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-2-furyl)urea;

- 5 173) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-methylsulfonylbenzyl)urea;
- 10 174) N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
- 5 175) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-chlorobenzyl)urea;
- 15 176) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-pyridinylmethyl)urea;
- 10 177) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,5-dimethoxybenzyl)urea;
- 20 178) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-pyridinylmethyl)urea;
- 15 179) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-trifluorobenzyl)urea;
- 25 180) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4,5-trimethoxybenzyl)urea;
- 30 181) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethoxybenzyl)urea;
- 35 182) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-dimethylaminobenzyl)urea;
- 40 183) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,5-dimethoxybenzyl)urea;
- 45 184) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(2-chloro-6-phenoxy)benzyl]urea;
- 50 185) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]urea;
- 55 186) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(3-hydroxy-4-methyl)phenyl]urea;
- 187) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(1H-benzimidazol-2-yl)phenyl]urea;
- 188) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
- 189) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-methyl-6-quinolinyl)urea;
- 190) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[4-(cyanomethyl)phenyl]urea;
- 191) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-quinolinyl)urea;

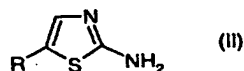
- 5 192) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1-oxo-2,3-dihydro-1H-inden-5-yl)urea;
- 193) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)urea;
- 10 194) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-oxo-5,6,7,8-tetrahydro-2-naphtalenyl)urea;
- 195) methyl-3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-4-methylbenzoate;
- 15 196) methyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)-3-methylbenzoate;
- 10 197) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(4-imidazo[1,2-a]pyridin-2-yl-phenyl)urea;
- 20 198) ethyl-4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoate;
- 15 199) (2R)-1-benzyl-2-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)propanamide;
- 25 200) 2-hydroxy-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)benzoic acid;
- 201) 2-chloro-5-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;
- 30 202) 3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino)benzoic acid;
- 20 203) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(5-methyl-3-isoxazolyl)urea;
- 35 204) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,6-dimethoxyphenyl)urea;
- 25 205) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,3-dimethoxybenzyl)urea;
- 40 206) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(3,4-difluorobenzyl)urea;
- 30 207) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2,4-dimethylphenyl)urea;
- 45 208) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(1H-benzimidazol-5-yl)urea;
- 35 209) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(R)-phenylglycinamido]urea;
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- 5 210) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-phenoxyacetamido)urea;
211) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[(S)-phenylglycinamido]urea;
10 212) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-(2-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl)urea;
213) N-(3-iodophenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
15 214) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-[3-(3-methoxy-1-propynyl)phenyl]urea;
215) N-(3-[3-(dimethylamino)-1-propynyl]phenyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
20 216) N-[4-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino]phenyl]methanesulfonamide;
217) 2-[3-(((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)amino]anilino]acetamide;
15 218) N-[3-(3-hydroxy-1-butynyl)phenyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
25 219) N-(imidazo[1,2-a]pyridin-2-yl-methyl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
20 220) 2-((((5-isopropyl-1,3-thiazol-2-yl)amino)carbonyl)(2-propynyl)amino)methyl]benzenesulfonamide;
30 221) N-(1H-indol-6-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
222) N-[(1S)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
35 223) N-(1H-indol-5-yl)-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
224) N-[(1R)-2-hydroxy-1-phenylethyl]-N'-(5-isopropyl-1,3-thiazol-2-yl)urea;
40 225) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-butylurea;
226) N-(5-isopropyl-1,3-thiazol-2-yl)-N'-benzoylurea;
227) N-(5-methyl-1,3-thiazol-2-yl)-N'-(2,6-dimethylphenyl)urea;
45 228) N-(5-methyl-1,3-thiazol-2-yl)-N'-benzylurea;
229) N-(5-methyl-1,3-thiazol-2-yl)-N'-butylurea;
35 230) N-(5-methyl-1,3-thiazol-2-yl)-4-morpholinecarboxamide;
231) N-(5-methyl-1,3-thiazol-2-yl)-N'-phenylurea;
50 232) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-methoxybenzyl)urea;

- 5 233) N-(5-methyl-1,3-thiazol-2-yl)-N'-(4-fluorophenyl)urea;
 234) N-[(1-ethyl-2-pyrrolidinyl)methyl]-N'-(5-methyl-1,3-
 thiazol-2-yl)urea;
 10 235) N-(5-methyl-1,3-thiazol-2-yl)-N'-(5-hydroxy-1H-pyrazol-
 5 3-yl)urea;
 236) N-(5-methyl-1,3-thiazol-2-yl)-N'-(3-pyridinyl)urea;
 237) N-(4-fluorophenyl)-N'-(5-methyl-1,3-thiazol-2-yl)urea.

15 14. A process for preparing a compound of formula (I), as
 10 defined in claim 7, which process comprises:

- a) when R_2 is a hydrogen atom
 reacting a compound of formula (II)

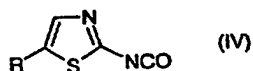


wherein R is as defined in claim 7, with a compound of
 25 formula (III)

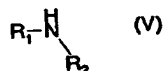


wherein R_1 is as defined in claim 7; or

- b) when R_2 is as defined in claim 7
 reacting a compound of formula (IV)

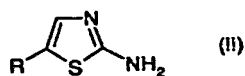


20 wherein R is as defined in claim 7, with a compound of
 35 formula (V)

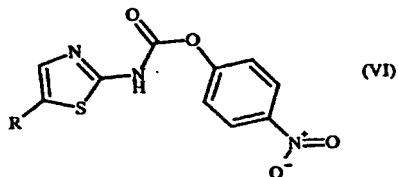


40 wherein R_1 and R_2 are as defined in claim 7; and, if
 25 desired, converting a 2-ureido-1,3-thiazole derivative of
 formula (I) into another such derivative of formula (I),
 45 and/or into a salt thereof.

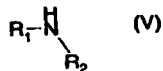
30 15. A process for preparing a compound of formula (I), as
 defined in claim 7, which process comprises reacting a
 50 compound of formula (II)



10 wherein R is as defined in claim 7, with 4-nitrophenyl-chloroformate, or a polymer supported form of it, thus obtaining a compound of formula (VI), or a polymer
5 supported form of it.



wherein R is as defined in claim 7; and reacting a compound of formula (VI) with a compound of formula (V)



10 wherein R₁ and R₂ are as defined in claim 7; and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (I), or a polymer supported form of it, into
30 another such derivative of formula (I), and/or into a salt thereof.

15 16. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, an effective amount of a compound
35 of formula (I) as defined in claim 1.

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INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/EP 99/08307

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D277/48 C07D417/12 C07D417/14 C07D471/10 C07D491/10 A61K31/426 A61K31/427 C07D471/04 //(C07D471/10,235:00, 221:00),(C07D491/10,317:00,221:00),(C07D471/04,235:00,221:00) According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used)																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>FR 7 428 M (MELLE-BEZONS) 12 November 1969 (1969-11-12) the whole document</td> <td>6-16</td> </tr> <tr> <td>X</td> <td>DE 15 67 044 A (PRODUITS CHIMIQUES PECHINEY SAINT GOBAIN) 13 August 1970 (1970-08-13) claims</td> <td>6-15</td> </tr> <tr> <td>X</td> <td>FR 2 252 808 A (ICI LTD) 27 June 1975 (1975-06-27) examples 1,6</td> <td>6-15</td> </tr> <tr> <td>X</td> <td>DE 20 40 580 A (MAY & BAKER LTD) 22 April 1971 (1971-04-22) claims</td> <td>6-15</td> </tr> <tr> <td colspan="3" style="text-align: center;">-/-</td> </tr> </tbody> </table>			Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	FR 7 428 M (MELLE-BEZONS) 12 November 1969 (1969-11-12) the whole document	6-16	X	DE 15 67 044 A (PRODUITS CHIMIQUES PECHINEY SAINT GOBAIN) 13 August 1970 (1970-08-13) claims	6-15	X	FR 2 252 808 A (ICI LTD) 27 June 1975 (1975-06-27) examples 1,6	6-15	X	DE 20 40 580 A (MAY & BAKER LTD) 22 April 1971 (1971-04-22) claims	6-15	-/-		
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* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family																				
Date of the actual completion of the international search 19 January 2000		Date of mailing of the international search report 04/02/2000																		
Name and mailing address of the ISA European Patent Office, P.O. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tr 31 651 epo nl Fax: (+31-70) 340-3016		Authorized officer Henry, J																		

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